UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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JOINT MEETING OF THE GASTROENTEROLOGY-UROLOGY DEVICES PANEL AND THE RADIOLOGICAL DEVICES PANEL

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September 9, 2013
8:00 a.m.

FDA White Oak Campus
Building 31, The Great Room (Rm 1503)
White Oak Conference Center
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

PANEL MEMBERS:

MARK TALAMINI, M.D.	Joint Panel Chair
ABDELMONEM A. AFIFI, Ph.D.	Member, G-U Panel
JAMES AHLGREN, M.D.	Temporary Member
KIMBERLY APPLEGATE, M.D., M.S.	Temporary Member
ALINE CHARABATY, M.D.	Temporary Member
DOUGLAS COLDWELL, M.D., PhD.	Temporary Member
EDWARD DAUER, M.D.	Temporary Member
RONALD FOGEL, M.D.	Temporary Member
AMY FOXX-ORENSTEIN, M.D.	Temporary Member
LEONARD GLASSMAN, M.D.	Temporary Member
PETER IMREY, Ph.D.	Temporary Member
KIM ISAACS, M.D.	Temporary Member
YULEI JIANG, Ph.D.	Temporary Member
DAVID KELSEN, M.D.	Temporary Member
TIMOTHY NOSTRANT, M.D.	Temporary Member
PAUL F. PINSKY, Ph.D.	Temporary Member
JEAN SHAPIRO, Ph.D.	Temporary Member
WILLIAM E. SHIELS, II, D.O.	Temporary Member

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ANDREW ZHOU, Ph.D.	Temporary Member
MARVIN ZISKIN, M.D.	Temporary Member
DAWN ALDRICH	Patient Representative
MILDRED D. FENNAL, Ph.D., RN	Consumer Representative
ELISABETH GEORGE, M.S.	Industry Representative
PETER LURIE, M.D., M.P.H.	Acting Associate Commissioner for Policy and Planning
LEE ZWANZIGER, Ph.D.	Designated Federal Officer

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OPEN PUBLIC HEARING SPEAKERS:

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Chair of ACR's Colon Cancer Committee
American College of Radiology

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SHUAI LENG, Ph.D.
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DAVID H. KIM, M.D.
Society of Abdominal Radiology

KIM RYAN
Director of Patient Information Services, Fight Colorectal Cancer

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M E E T I N G

(8:00 a.m.)

DR. TALAMINI: Good morning, again. It's approximately 8:00 a.m., and I would like to call this Joint Meeting of the Gastroenterology and Urology Devices and Radiologic Devices to order.

My name is Dr. Mark Talamini, the Chairperson of this Panel. I am a Professor of Surgery at University California, San Diego, a gastroenterology surgeon.

I note for the record that the voting members present constitute a quorum, as required by 21 C.F.R. Part 14. If you have not already done so, please sign the attendance sheets that are on the tables by the doors during a break.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. And if we could begin with Dr. Lurie at this end of the table and go clockwise please.

DR. LURIE: Hi. I'm Dr. Peter Lurie. I'm the Acting Associate Commissioner for Policy and Planning here at FDA.

DR. IMREY: I'm Dr. Peter Imrey. I'm at Cleveland Clinic, Case Western Reserve University. I'm a biostatistician and sometime epidemiologist.

DR. APPLEGATE: Good morning. I'm Dr. Kimberly Applegate,

and I am a radiologist at Emory University.

DR. CHARABATY: Good morning. I'm Aline Charabaty, Dr. Charabaty, from Georgetown Hospital, Washington, D.C. I'm a gastroenterologist.

DR. AFIFI: I'm Dr. Adbelmonem Afifi. I am Professor Emeritus of Biostatistics at the School of Public Health at UCLA.

DR. FENNAL: Good morning. My name is Dr. Mildred Fennel, and I am the Director of the International Nursing Education Consortium, and I'm the Consumer Representative.

DR. NOSTRANT: Hi, Tim Nostrant, Professor of Medicine, GI, at the University of Michigan.

DR. COLDWELL: Good morning. I'm Doug Coldwell. I'm a Professor of Radiology and Bioengineering at the University of Louisville and head of Interventional Radiology.

DR. FOGEL: Good morning. I'm Ron Fogel, a gastroenterologist in private practice in Detroit, Michigan.

DR. PINSKY: Paul Pinsky. I'm Acting Chief of the Early Detection Branch at National Cancer Institute.

MS. GEORGE: Hello, I'm Elisabeth George. I'm with Philips Healthcare. I'm the Vice President of Global Regulations and Standards, and I'm here today as the Industry Representative.

DR. SHAPIRO: Hi, I'm Jean Shapiro. I'm a cancer epidemiologist

at the CDC in Atlanta.

DR. DAUER: Good morning. Dr. Edward Dauer, a diagnostic radiologist and biomedical engineer. I'm a Research Associate Professor at the University of Miami in Florida.

DR. ZWANZIGER: I'm Lee Zwanziger. I work in the FDA, Office of the Commissioner, Office of Planning, Risk Communication Staff. I am the DFO for this meeting.

DR. FOXX-ORENSTEIN: Good morning. I am Dr. Amy Foxx-Orenstein. I'm a gastroenterologist at Mayo Clinic in Arizona.

DR. GLASSMAN: I'm Dr. Len Glassman. I'm a diagnostic radiologist in private practice in Washington, D.C. I'm also Clinical Professor of Radiology at GW, and a Section Chief at the American Institute for Radiologic Pathology.

DR. ISAACS: Kim Isaacs. I'm a gastroenterologist and Professor of Medicine at the University of North Carolina.

MS. ALDRICH: Dawn Aldrich, CEO of Solutions Cancer Resource Center, New York.

DR. JIANG: Yulei Jiang. I'm Associate Professor, Radiology at University Chicago and medical physicist.

DR. STEINBERG: I'm Dr. William Steinberg. I'm a practicing gastroenterologist at Rockville Internal Medicine Group, which is a correction of what it says on the roster here. I'm Clinical Professor of Medicine at

George Washington University.

DR. AHLGREN: James Ahlgren. I'm a medical oncologist and Professor of Medicine and Pharmacology at George Washington University.

DR. ZISKIN: I'm Marvin Ziskin. I am the Emeritus Professor of Radiology and Medical Physics at Temple University in Philadelphia.

DR. KELSEN: David Kelsen. I'm a medical oncologist from Sloan-Kettering in New York.

DR. TALAMINI: Thank you very much.

Dr. Zwanziger, the Designated Federal Officer for this meeting, will make some introductory remarks.

Dr. Zwanziger.

DR. ZWANZIGER: Thank you, Dr. Talamini.

The Office of the Commissioner of the Food and Drug Administration is convening today's joint meeting of the Gastroenterology-Urology Devices Panel and the Radiological Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Act of 1972. With the exception of the industry representative, all members and consultants of the panels are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of the Panels' compliance with Federal ethics and conflict of interest laws covered by, but

not limited to, those found at 18 U.S.C. Section 208 is being provided to participants in today's meeting and to the public.

FDA has determined that members of these Panels are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members of these Panels have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Today's agenda involves the risks and benefits of computed tomography colonography for screening of asymptomatic patients for colorectal cancer. This is a particular matters meeting during which general issues will be discussed.

Based on the agenda for today's meeting and all financial interests reported by committee members, no conflict of interest waivers

have been issued in connection with this meeting.

With respect to FDA's invited industry representative, we'd like to disclose that Ms. Elisabeth George is participating in this meeting as a non-voting industry representative, acting on behalf of the interests of all related industry. Her role at this meeting is to represent these industries in general and not any particular company. Ms. George is employed by Philips Medical Systems.

We'd like to remind committee members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationships they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during this meeting and will included as part of the official transcript.

Today's Joint Panel meeting includes temporary members, as listed in the meeting roster, in each packet, and on our website. For the record, these special Government employees have undergone the customary conflict of interest review, and they have reviewed the materials to be considered at this meeting.

Before I turn the meeting back over to Dr. Talamini, I'd like to make just a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Inc., at 1378 Cape St. Claire Road in Annapolis, Maryland, 21409. And their telephone number is 410-757-6337.

Information on purchasing videos of today's meeting can be found at the FDA meeting registration table.

The press contact for today's meeting is Erica Jefferson, who's standing there in the back. Thank you.

And I'd like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area behind the red ribbons.

I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you're presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with AnnMarie Williams at the registration desk or one of her colleagues there.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time you speak. Please do use the microphones. Turn them on before you speak and turn them off when you're finished.

Restrooms are located down the hall to the right of the main lobby, and there is also a kiosk for beverages and light food in the main lobby.

Finally, let's all please silence our cell phones and other electronic devices, and thank you for your attention.

And now let me turn back to Dr. Talamini.

DR. TALAMINI: Thank you, Dr. Zwanziger.

We will next hear from Dr. Peter Lurie, Acting Associate Commissioner for Policy and Planning, Office of the Commissioner, FDA.

Dr. Lurie.

DR. LURIE: Good morning, and welcome to White Oak. I want to assure everybody from out of town that this is as good as weather ever gets in Washington, so enjoy it while you can.

As you know, this is a Joint Meeting of the Gastroenterology and Urology Devices Panel and the Radiology Devices Panel, both of which belong to the Medical Devices Advisory Committee. But this meeting is being convened by the Office of the Commissioner, which is where I work.

The purpose of the meeting today is to discuss current evidence of the risks and benefits of CT tomography colonography, hereinafter CTC, I think for all of us at this meeting, for screening of asymptomatic patients for colorectal cancer.

The Joint Committee will provide advice that will assist FDA's consideration of the evolving research on this topic and will inform the

Agency's continuing regulation of these devices.

Let me provide just a little background for the meeting. As you all know, FDA began clearing devices for CTC in the early 2000s. But recent efficacy and safety data, for example, the ACRIN trial and others about which we will hear today, were not available when these devices were first marketed for screening. They were also not available when in 2008, 2009, several comprehensive reviews of the risks and benefits of CTC screening for colorectal cancer by outside groups appeared and which reported differing recommendations. And you'll hear about those differing recommendations as well.

As a consequence, Commissioner Hamburg decided to seek expert advice on the risks and benefit of CTC for screening asymptomatic patients in the light of these evolving data.

As important as knowing what this meeting is about is also knowing what it is not about. This is a meeting that is exclusively directed to scientific matters and is focused on technologies and types of screening as a whole. As such, we do not expect the Panel to address particular devices or particular PMAs, premarket approval applications, or 510(k)s, another route to approval in this country for medical devices. Nor do we expect the Panel to address the regulatory status of specific CTC devices or any other CRC screening modality.

As many of you know, our statute does not provide for

consideration of cost effectiveness or even cost for that matter. And so, those are really not part of the charge to the committee today.

So this brings us to the questions before the Panel, which are up on the screen either in front or above you. And I'll go through them verbatim, but emphasizing the parts that are most important.

Considering available colorectal screening tools and current colorectal cancer screening recommendations, please discuss the currently available data and information on:

Firstly, the potential benefits of CT colonography for the screening of asymptomatic patients for colorectal cancer, including test performance characteristics, impact upon overall numbers of patients screened, and extracolonic findings;

And, secondly, safety issues related to the use of CT colonography for the screening of asymptomatic patients, again, for colorectal cancer, including radiation risk and extracolonic findings.

So you see extracolonic findings in both the benefit and the safety side of the equation.

And then, finally, Question No. 2, which asks you to in effect weigh A against B. Given the risks and benefits identified, please discuss your views on the role of CT colonography as one option for screening asymptomatic patients for colorectal cancer.

We do not anticipate a direct up or down vote on this the way

some of you might be accustomed to from other Advisory Committees, but quite possibly a consensus of views might emerge from the meeting nonetheless.

After the meeting, the advice that you provide will be provided to the Commissioner, as well as to the Center for Devices and Radiological Health, to inform the Center's ongoing regulation of CTC.

And with that, I hand it over to Dr. Talamini, who will chair the meeting. Thank you all for attending.

DR. TALAMINI: Thank you, Dr. Lurie.

We will continue. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

Next, I'd like to introduce our first guest speaker, Dr. Michael Pignone, Professor of Internal Medicine, University of North Carolina-Chapel Hill.

And just a note to the Panel, obviously a lot of information to be presented this morning. We certainly appreciate your focus as we look at all of this data. And we'll have the opportunity to discuss it fully this afternoon.

So with that, Dr. Pignone.

DR. PIGNONE: Thank you. I appreciate the opportunity to present to the Panel. I'm going to give an overview of colorectal cancer

screening.

Is the microphone on? Can you guys hear me?

DR. TALAMINI: Yes.

DR. PIGNONE: Okay. Thanks.

First, for my disclosure, I have in the past given talks on CT colonography for the American Society of Clinical Oncology and the Royal College of Surgeons. And probably more germane, I'm a member of the U.S. Preventive Services Task Force. However, the views today are mine only and not the views of the U.S. Preventive Services Task Force. I wanted to make that clear.

So I'm going to start with my conclusions, and we'll work our way back to that. The key messages for today -- I think as most of you are already aware, colorectal cancer is an important health problem for U.S. adults, particularly those over age 50. Screening by a number of different modalities can reduce the incidence of colorectal cancer and mortality from colorectal cancer. And persons ages 50 and over should be screened, and there are several effective screening tests available. However, current evidence by my interpretation does not suggest one test is superior to others, and patient preferences matter. So those are the conclusions. Let's work our way through that.

Let's start with the burden of disease. Colorectal cancer remains the second leading cause of cancer death in the United States. The

data from the CDC from 2009 suggests about 135,000 new cases were diagnosed in that year. And that's coming down a little bit, and that's just about 50,000 per year. Now, the incidence and mortality have been decreasing over time, which is a good thing. And I'll show you that in graphic form here.

So this again is data from the CDC, and this is colorectal cancer incidence on the left for men, on the right for women, and stratified by race/ethnicity. And we can see here that there's a clear trend towards lower incidence and lower mortality that's been present even before the years shown here on the graph, which go back about 15 years. Unfortunately there remain considerable racial and ethnic disparities with African-Americans continuing to have higher rates in both incidence -- and I'll show you in a second mortality -- but all groups moving in the right direction in terms of decreases.

This is incidence. Here's mortality again: men on the left, and women on the right. And, again, you can see that overall men are at a little bit higher risk for colorectal cancer mortality, and that African-Americans, both men and women, are at higher risk for mortality than their counterparts in other racial/ethnic groups. But, again, for all groups the trend is basically moving in the right direction with a lowering colorectal cancer mortality. And, again, this trend goes back considerably before the years shown here on this graph.

It's important to note the topic for the meeting today is asymptomatic patients. And, again, for colorectal cancer, most of the cases of colorectal cancer arise in people at average risk, so somewhere between 65 and 85% of colorectal cancers are felt to be sporadic, arising in people that are not at increased risk. Probably 10, 20, maybe even as high as 25% of cases arise in people that have a family history either of colorectal cancer or adenomatous polyps. And then a small proportion of cases, somewhere between 5, maybe 7%, arise in people with clear genetic syndromes, including hereditary non-polyposis colorectal cancer, HNPCC, and then a variety of more rare syndromes, including familial adenomatous polyposis, which again accounts for a small proportion of cases, but quite high risk in the people who have the syndrome.

So, again, the important point here is that most of these cases are arising in average risk patients, not people at high risk. And, therefore, it's not possible just to identify a small segment of the population for screening. We really have to screen broadly.

Here are current colorectal cancer screening options. Perhaps the first technology that was proven to be effective, fecal occult blood testing, a test that is administered annually, or perhaps every two years. There are more than one technology, and, in fact, the number of technologies for fecal occult blood testing is growing. The more traditional test would be the guiaic-based gFOBT, which I'll refer to in the future. And then the more

recent testing has been with fecal immunochemical testing, or FIT, a newer technology. We also have flexible sigmoidoscopy, which can be performed every five years, the combination of fecal occult blood testing and flexible sigmoidoscopy, colonoscopy, generally recommended to be performed every 10 years, and CT colonography perhaps every five years.

Now, I think it's important as we go through not just to talk about the test, but really about the screening strategy, which involves both the test and also the interval at which the test would be performed. And that's why I put this in the slide early on so we can kind of have the conversation from that point of view because, again, it's not just the test, but the interval as well that becomes important.

So a little bit about fecal occult blood testing. This is an example of fecal occult blood test. It has a number of advantages, including being performed at home, but has to be performed more frequently than some of the other modalities.

We have strong data on the effectiveness of fecal occult blood testing. I show here data from three randomized trials: one in the United States, the Minnesota trial; two from Europe, the UK and Denmark trials. All of them are randomized controlled trials of either annual or biennial every two year fecal occult blood testing. These are all done with guiaic-based fecal occult blood tests, older technology. They had follow-up that ranged from 8 to 18 years. In some of the cases the slides were rehydrated prior to being

developed, which increases the sensitivity but lowers the specificity.

And you can see across the board here that the percentage of patients requiring colonoscopy varied across the different studies from as low as 5% to as high as 30%. The mortality reduction from colorectal cancer in the trials also ranged from 15 to 33%. In the Minnesota trial the incidence reduction was reported to be either 17 or 20%, with extended follow-up based on reduction in cancers, probably from the polypectomies that resulted from the original colonoscopies done in that trial.

Moving on to flexible sigmoidoscopy, another technology that has been well studied. This is a picture of a flexible sigmoidoscope here. And I just bring up an anatomic diagram of the colorectal region, remembering that sigmoidoscopy visualizes about a third of the colon and therefore is not visualizing the entire area at risk for colorectal cancer, but yet is a useful screening test nonetheless.

We know this from a couple different levels of evidence. For quite some time we've had good evidence from a well-designed case control study performed in the Kaiser Permanente system that showed a 59% reduction in deaths from colorectal cancer within the reach of the sigmoidoscope, and no reduction in deaths from proximal cancers. So the idea here was that there was good controlling for potential confounders based on the lack of difference in deaths in the proximal cancers, but a rather large reduction in colorectal cancer death for the ones that were within reach

of the sigmoidoscope.

That was our level of evidence that we had available to us up until the last several years. In the last several years two randomized controlled trials have been published. The first, the UK trial, was a trial of one-time sigmoidoscopy performed in the UK by Wendy Atkin and her group that showed decreased incidence of colorectal cancer by 23% and decreased mortality by 31% in people participating in this one-time sigmoidoscopy at age 60 study.

Soon thereafter, we had the reports from the PLCO trial, a trial performed in the United States as part of a larger cancer screening trial. And in this trial, sigmoidoscopy at three- to five-year intervals decreased incidence by 21% and mortality by 26%. So relatively consistent findings across the two randomized trials that were probably consistent with, though not as large in magnitude as the observational evidence that was cited there.

Now, the 59% was only the cancers within the reach of the sigmoidoscope in the observational study, and there is similar reductions in cancers within reach of the sigmoidoscope in the randomized trials, so I think a pretty strong and consistent body of evidence that showed effectiveness of endoscopic screening with flexible sigmoidoscopy.

DR. TALAMINI: Dr. Pignone, if could just ask you to pause for a moment. We're getting some annoying interference that requires you to be quiet for a moment so that we can hopefully address it.

Well, why don't you go ahead to your next slide, and then we may ask you to pause again after that.

(Pause.)

DR. PIGNONE: Yeah, that was our pregnant pause to consider the evidence. That's actually a good stopping point because really the fecal occult blood testing and the sigmoidoscopy evidence is the ones that are best supported by randomized controlled trials.

(Pause.)

DR. PIGNONE: Thank you. Is that on? Okay.

So we're going to turn now to the evidence from our other technologies. We'll start with colonoscopy. And I'll start by saying that colonoscopy is part of the screening cascade for both FOBT and sigmoidoscopy. If you have positive screening tests, you go on to have a diagnostic colonoscopy as part of the workup.

Here we're looking at colonoscopy being used as the initial technology. It is the most accurate single test for the detection of polyps and colorectal cancer; however, there are also other considerations to be taken into account. Another positive feature of colonoscopy is it's a one-step screening and treatment procedure, so that you don't necessarily have to go on and have the second test after the initial test. Unfortunately, to date there are no completed trials of screening colonoscopy with mortality or disease incidence as endpoints. There are plenty of diagnostic accuracy

studies and some randomized trials, particularly those in Europe and in the VA system that are ongoing right now. But we don't have good randomized controlled trial evidence to pin down the exact incidence and mortality reduction from screening with colonoscopy.

There are case-control observational studies that suggest a decreased incidence of about 50% and a decreased mortality perhaps as high as 70% or more from the use of colonoscopy as opposed to lack of use of colonoscopy, which again, like the earlier evidence in sigmoidoscopy support the effectiveness of screening but probably aren't definitive. So that's where things stand for colonoscopy.

I'm going to leave the discussion about CT colonography to later talks, but we'll say that there are certainly diagnostic accuracy studies of CT colonography that suggest that it can be accurate as well. And you guys will hear much about that later.

A lot of the work I do looks at implementation of colorectal cancer screening, and one of the questions that comes up is with all these different options, how do we put that all together and come up with a strategy that's right for patients and providers? Unfortunately, there aren't any head-to-head trials that compare the different technologies. So we have evidence from randomized trials for FOBT and sigmoidoscopy. We have good accuracy studies and observational studies for colonoscopy and CT colonography. And, really, in order to compare the different technologies,

you're left with statistical modeling to compare the effects.

I'm going to show you a little bit about that on the next slide -- next couple slides, and then we'll go on from there to some of the other practical considerations.

So, we did for the U.S. Preventive Services Task Force in 2002 a systematic review of modeling studies. And at that point in time -- and really things haven't changed since then -- we found that FOBT, sigmoidoscopy, and colonoscopy are all likely to be quite effective compared with no screening, but that no single strategy was clearly either the most effective or favored compared with others.

In those modeling studies, sigmoidoscopy oftentimes was slightly less effective than the other technologies, especially when compared against the new fecal occult blood tests. But, again, both in 2002, and then more recently when we've updated that kind of review work, there's still no clear optimal strategy among the different strategies. And, in fact, our level of uncertainty about the specific effects really kind of puts them all into one area.

This is an example of that. This is data from the MISCAN model courtesy of Iris Lansdorp-Vogelaar from the Netherlands, who is part of the NCI-sponsored CISNET collaborative. This is a nice modeling group that's done very good work. I think it's probably the state-of-the-art work in simulation modeling. And here in the expected incidence and mortality

reductions from colorectal cancer screening in adults ages 50 to 80, you see the different technologies in the first column, the incidence reductions that are anticipated with use of those technologies in the second, and the mortality reductions anticipated with those technologies in the third.

And you see, I guess, first of all, the most important thing is that you can expect incidence reductions between 40 and 56%, and mortality reductions in the 60 and 70% range with any of these technologies compared with no screening. But, again, these numbers are pretty close together, and we don't have enough data to really be able to say that one is precisely better than the other.

So in the absence of data saying there's clearly greater benefits from one technology to the other, we have a number of other factors that might factor into the decision about whether to choose a particular strategy or not for patients and providers. These include test availability -- you really can't offer a test if it's not available to you in a reasonable geographic range around where you live. The particular benefits and harms of each tests -- so the tests have different adverse effect profiles. We'll talk about that some today.

The difference between home testing or traveling to go have your test, depending on the patient and their situation, that may be an important consideration. And then, of course, the frequency, which ranges from annual testing for fecal occult blood testing up to every 10 years. And

these may be things that are important to patients. So, clearly patient preferences are important.

Cost is not really a purview of the discussion today. One of the nice things on the policy front is with the Affordable Care Act in the United States, we now have mandated coverage for each of these technologies without a co-pay, if it's considered to be an effective technology. So that's a good general development for this area and a number of other preventive care areas.

Oftentimes people ask me, well, should we just tell people what to do or should we offer them a choice? We haven't had strong evidence to inform that question until recently. A nice study by John Inadomi and colleagues from San Francisco, though, compared the strategy of offering everyone fecal occult blood testing, offering everyone colonoscopy, or offering a choice of those two modalities.

And in their study, those who were offered choice or who were offered FOBT only were more likely to end up being screened compared with those offered colonoscopy only. That's an interesting finding but bears further study and needs to be replicated before I think we say that this is a definitive finding. It also only addresses the initial round of testing, and an initial round of colonoscopy is closer to a full screening strategy of colonoscopy than an initial round of fecal occult blood testing, which needs to be repeated every year or every other year going forward. So it's not

exactly equivalent results, but somewhat helpful I though.

Bernard Levin is going to talk much more about current recommendations. I just wanted to mention that a number of different bodies have offered recommendations about colorectal cancer screening. And the Preventive Services Task Force recommends using fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults ages 50 to 75, and gives its highest recommendation, a Level A recommendation. It found insufficient evidence to assess the benefits and harms of CTC and issued an (I) recommendation when it made its last recommendation statements in I believe 2008-2009.

The American Cancer Society recommended fecal occult blood testing, sigmoidoscopy, colonoscopy, CTC, barium enema, or stool DNA testing with a preference for the structural exams. And both recommendations emphasized the importance of considering patient preferences. So more to come on that later.

However, our current screening rates in the United States are still not optimal. This is a map of data from the CDC BRFSS survey, which is a telephone-based household survey of a number of different health factors, and this is colorectal cancer. We've made a lot of progress. Overall 64% of U.S. adults ages 50 to 75 are up to date with screening for colorectal cancer by any modality. But, again, that's about two-thirds up to date and about a third who are not up to date, so there's still some room to go. And you can

see that there's substantial geographic variation with more screening in the Northeast and upper Midwest, perhaps in the State of Washington as well, and then some of the areas, particularly in the South Central area lagging behind in terms of screening rates.

There are a number of effective ways of increasing screening. Technologies like providing data back to providers, providing reminders to providers or patients, the use of decision aids or patient education tools, and then strategies to reduce barriers to screening all have been shown to be effective in increasing colorectal cancer screening rates. This is definitely an area where some difference can be made. These technologies -- or these different potential interventions are discussed in the Community Guide for Preventive Services, which I've referenced here. And they update that work regularly, in case you're interested in more about that.

So, again, finally, just to come back to the key messages, colorectal cancer is an important health problem for U.S. adults over age 50, screening reduced colorectal cancer incidence and mortality, and people over age 50 should be screened. To my reading of the literature, there's no single best test, and patient preferences matter and should be incorporated in decision-making. Thank you.

DR. TALAMINI: Thank you, Dr. Pignone.

Next we'll hear from Dr. Duncan Barlow, Department of Medicine, Uniformed Services University of Health Sciences.

DR. BARLOW: I want to thank the Panel for inviting me to present here. Is that on?

My name is Duncan Barlow. I'm the Senior Radiologist with the Colon Health Initiative at Walter Reed National Military Medical Center. The only disclosure I have to make is the views expressed in this presentation are mine and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.

My objectives today are to provide a brief history of the Colon Health Initiative at Walter Reed National Military Medical Center and then provide a detailed description of our approach to CT colonoscopy screening as we perform it at Walter Reed.

The Colon Health Initiative was established by a congressional grant in 2004. The purpose was to improve colorectal cancer screening in the national capital region through integration of CT colonography into an active GI practice. We're also supposed to optimize the use of optical colonoscopy for therapy, by screening educate beneficiaries about colorectal cancer and the screening options available to them, and a new purpose is also to improve colorectal cancer screening to remote military treatment facilities that do not have adequate gastroenterology or general surgery support through a teleradiology network.

Colon Health Initiative results to date. We've screened over 15,000 patients: 1,740 of these patients or about 12% were found to have

one or more polyps; 1,455 patients or about 10% had significant extracolonic findings resulting in further studies. Of those, we discovered 69 new extracolonic cancers, and they include primary lung cancers, mesothelioma, hepatocellular carcinoma, pancreatic cancer, renal cell lymphoma, and ovarian cancer.

As far as the teleradiology network goes, we're right now providing services to multiple smaller MTFs: Naval Hospital Jacksonville, DeWitt Army Medical Center, Kimbrough Army Medical Center, and we're now bringing online San Diego Medical Center and also Naval Hospital Camp Pendleton.

Here's an example of some of the extracolonic findings we have found in our studies. The upper left slides shows a primary lung cancer in the left lung base. Upper right-hand slide shows a mass arising off the inferior pole left kidney. That was a renal cell. The lower left hand shows a fat, soft tissue and bone containing a left ovarian teratoma, and lower right shows an infrarenal abdominal aortic aneurysm, all silent, and these were on healthy walkie-talkie patients that presented for colorectal cancer screening.

What have we seen in the national capital area because of CTC? We see here we've seen a significant increase in the colorectal cancer screening. This is the HEDIS scores for colorectal cancer screening compliance. If you add in the VCs that we've done, you can see a steady increase since 2006 in the colorectal cancer screening compliance.

This is one of our own internal studies we did. This is where we interviewed 250 patients as they hopped off the VC scanner and basically asked them questions about their experience. The significant one was would you have started down the colorectal cancer screening pipeline if CT was not available? Thirty-seven percent of them answered no, they would not have entered into colorectal cancer screening if that option had not been available to them. Fifty-seven of these patients had actually experienced both a optical and VC. And, basically, when asked which did they prefer, a high percentage, 97%, preferred the CT colonography.

That being said, let's talk about the components of a successful CT colonography program as we see it at the Walter Reed. The needs are:

Adequate bowel prep -- that includes colon cleaning with a cathartic followed by stool and fluid tagging; accurate colon distension -- we use a CO_2 mechanical insufflator. I think that's a must; CT technique -- we use a multi-detector CT with low dose imaging; the 3D modeling software; and then basically adequate radiologists that can interpret and report either using a 3D or a 2D polyp detection scan pattern.

As far as bowel prep goes, a laxative is used for bowel catharsis to reduce the stool burden. We use CT to tag the residual stool. We use a water soluble contrast agent to tag residual fluid. No bowel prep is ever complete. And the gastroenterologists and the general surgeons can basically aspirate any residual stool or fluid, get to the colon wall, and look for the

pathology. We in the virtual world must electronically subtract it out, so we have to tag the residual stool and fluid. And you can see the difference between the two. The inferior slide is a poorly prepped colon. The stool burden is too great. The tagging agents cannot basically successfully tag the stool and cannot be subtracted out. The patients are also put on a clear liquid diet the day before the examination to reduce the stool burden.

The prep that we use at Walter Reed consists of MoviPrep, that's the cathartic, CT barium, and then Gastroview. It's a very simple prep. They start at 4:00 p.m. with the catharsis, at 9:00 p.m. they drink the CT barium for tagging the stool, and then at 10:00 they drink the Gastroview to tag the residual fluid.

We use MoviPrep. It is a polyethylene glycol solution. It's an osmotic laxative, but it's gentle and it's safe for use in patients who cannot tolerate significant fluid shifts or electrolyte shifts. We have a lot of patients that have hypertension, they have renal and cardiac insufficiencies, they're on a multitude of meds, and so we basically prefer to use this. This is also what the gastroenterologists use for their optical colonoscopies. It's easy to follow instructions for mixing and consumption, and it is palatable.

The residual stool is tagged with CT weighted barium. That's 2% weight per volume of barium. It's the appropriate density for CT imaging, it tags the residual stool for electronic subtraction, and it does not prohibit follow-on optical colonoscopies. We have at our institution the same day

read where the patient can come in and have the VC done. If there's significant findings, if they opt for it, they can go onto an optical. So our gastroenterologists are used to performing optical colonoscopies with the barium on board, and it doesn't preclude or complicate the examination. This is a single dose. They have to drink two-thirds of the bottle, real easy. It's very palatable. It tastes like a smoothie.

The fluid tagging is done with Gastroview. This is a water-soluble iodinated contrast agent. It tags the residual fluid for electronic subtractions. It's hyperosmolar, so it also draws fluid into the colon and then serves as a wetting agent limiting any adherent stool to the colon wall. So it actually helps keep the adherent stool off the wall of the colon. It's a single dose. They got to drink the whole bottle. This is the least palatable of the entire prep. This is the one they usually complain about. But there again, if you chug it, you can get it down and it's easy to use.

As far as colon distension, we do use a mechanical CO_2 insufflator. When we first started out back in 2004, we were using room air with a bulb insufflation, and we had a lot of patients that basically did a lot of cramping. We had two people vasovagal. Since we moved over to the CO_2 insufflation with the pump, it is a very gentle pump, it raises the pressure up into the colon in four easy steps up to 25 psi and then maintains it. And as you can see here in these two pictures, no matter how redundant the colon is, it does a very good job of distending that colon up. I wish all my old BEs

looked like that basically since we started using the pump.

It's a slow steady insufflation, and it reduces spasm during the procedure. The CO_2 is absorbed across the colon wall so it reduces discomfort after the procedure. It's a rectal catheter. The balloon is much smaller than the old Bordex tip that we used for the old barium enemas, and it's one time use and throw it away. So you don't have any problems with contamination.

CT scanning technique. We have a 64-slice. That may be a little overkill. The majority of the DOD trials were done on a 4-slice. A 16-slice is adequate. I mean most of your hospitals have the higher end CT scanners, and so that's what we use at Walter Reed. We use thin collimation, 1.25 mm collimation at a 1 mm interval. We use a reduced technique, 30-40 mAs. We may bump it up a little bit for the morbidly obese patients, but that's our usual standard dose. We do two runs: supine and prone. And, basically, the radiation dose is between 3-6 mSv, which is equivalent to about four or five plain film views of the abdomen. You spread that over five years. If you have a negative VC, you come back in five years. That's not a significant dose.

The tradeoff is the visualization. If you look here, that's a standard abdominal pelvic CT scan, the two upper slides with IV contrast high dose technique. The bottom two slides are the VC. It's a much grainier image; however, you can pick up extracolonic findings. You don't need the

high dose technique to build an exquisite 3D model.

CT modeling software. Basically, there are a whole bunch of vendors out there and basically pretty much similar. We do a primary 3D endoluminal evaluation. That means we fly through the 3D model, the colon, and do our preliminary findings for colon pathology, and then we look to the 2D images to verify. So we are a primary 3D fly-through with a 2D verification. Other institutions prefer the 2D as a primary, but then use a 3D to verify. And it really doesn't matter which technique you do. You just should use both of them for correlation. You should use 3D first with 2D verification or vice versa.

We also at Walter Reed synchronize the two fly-throughs. This is something that we had the vendor do for us so that when we fly through the colon, we are actually looking at two windows and we fly through synchronously. That makes it an easy check for artifacts. The majority of the findings on VC happen to be artifacts. You have to sift through the forest to find the trees. And, basically, when you have a synchronized fly-through, we find it easier to basically verify what is artifactual because it changes between the two fly-throughs.

The additional interrogating tools that you can -- some of the softwares have this and we use this -- the color window or transparency rendering tool. It assigns a color to specific CT attenuation values. It allows for a quick check of internal densities, i.e., tagged stool will have small

microbubbles of air in it and fecal fat, whereas a polyp will be pretty much uniform in its soft tissue attenuation.

You also have the luminal coverage tool. This tracks through direct line of sight mapping. As you fly through the colon, it basically maps out what surface of that colon was included in the field of view. And it's very, very helpful because you can fly through the colon, and basically in some of the deep folds, you may have missed a section. The same tool has a missed region tool, which allows you to go back and systematically hit all those points that were not included in the field of view when you flew through. So this documents -- you can document 99% visualization of the entire endoluminal colon surface.

Here's some of the common artifacts that basically we have to deal with. And there again, the trick to reading VC is to basically find what is artifact, dismiss it, and then not refer a patient on to an optical for it. The first is a subtraction artifact. The algorithm that subtracts out that tagged stool and fluid is not 100%. It leaves an irregularity in the wall. And depending upon whether it's barium, the tagged barium on either side of a fold, you have a significant defect. And basically that can look like an ulcer, it can look like a polyp. You need to be able to differentiate that and say that's artifact and move on and not call it.

Here's an example. On the left you can see the subtraction artifact. Now, that's very minor, but it's due to that pool of barium sitting on

the posterior wall of the rectum. And, basically, when the patient is run prone, the fluid goes elsewhere, and the tagged stool and barium goes elsewhere to a different side of the colon. And then basically on the opposite run, on the prone run you can see that that's pristine, smooth colonic mucosa. So that's an artifact; you'd go right by that and wouldn't call that.

This is the mobile polyp. This a piece of stool that basically you can see the ileocecal valve on the back side and that polyp, that pseudo-polyp or piece of stool has fallen to either side of the ileocecal valve when being positioned in a prone and supine run.

Here is adherent stool. And there again, you use your accessory tools. You put the color window on it. You can see that there's internal fat in that. You look at the 2D images, and you can see there again by the attenuation there's a little bit of fat and air in it. On the right side, there's a bubble that's basically in a solid filled segment of descending colon. And, basically, you can see it has the attenuation or the color window of air. And on the 2D you can see it's just a submerged bubble.

This is a sample fly-through I'll basically kind of show you. Starting in the rectum that's the rectal tube. There's some stool on the side of the rectum, but I mean if the patient is adequately prepped and has followed the prep right, if the colon is distended right, you get a run like this. And this was a 51-year-old asymptomatic male that came in for simple colon cancer screening. That's a 3 cm pedunculated polyp in the sigmoid colon.

You put the color window on it, and you can see that it is soft tissue density solid. You fly around it, measure it, and then move on.

There's more stool. There's some subtraction artifact on the left hand side of the wall of the colon. And we fly up, seeing the front side of the folds, we fly back seeing the backside of the folds.

Almost done. There we go. We use the priority pictorial report that comes with the 3D modeling software. All of them have it. Basically, we pattern the report after the GI colonoscopy report. We will take standard views of segments of the colon. We will take images of the ileocecal valve on both the prone and supine run to document we got around the horn on both runs. We will then take picture of any significant colonic findings. We take 3D images, the 3D endoluminal images with the measurements. We take the 2D confirmation views and put the color window on it, and then we describe any extracolonic findings.

We do use the C-RADs lexicon when reporting out the findings. This is a standardized reporting system based on the success of the BI-RADs with mammography. It breaks it down into colon findings and extracolonic findings, and it basically starts with C0, which would be your inadequate study or incomplete study, all the way down to your colonic mass.

And here's some examples of that. The normal colon is a C1. That'll be no visible abnormalities or polyps less than 6 -- mucosal abnormalities less than 6 mm. And then lipomas, diverticuli, things like that,

that's normal old age colon. The intermediate polyp is between 6 and 9 mm. If you have less than 3, then that's a C2. C3 are significant polyps -- that's greater the 10 mm -- or three or more intermediate size polyps. And then C4 is your colonic mass likely malignant.

Here's some examples of C1 and C2 findings. On the left-hand side, this is a lipoma. If you look at the lower left-hand slide, you see that this is uniformly fat attenuation. You can put a Hounsfield unit interrogation window on that, and basically that's what it looks like endoluminally. When we first started, we were reporting these things out and the patients were going to optical colonoscopy for it. Every one of them turned out to be a lipoma on colonoscopy, and so the gastroenterologists asked us to stop referring it. If we see that, we call it a lipoma, and it is a C1.

Here's an intermediate size polyp, and it's 6 or so millimeters. It's off a fold in the mid-transverse colon. You can see it on the 2D images. This is a larger polyp, an hepatic flexure. This is a significant polyp greater than 10 mm. And then the slides on the right are what you don't want to see. This is an apple core adenocarcinoma of the sigmoid colon.

Likewise, the extracolonic findings are reported out in a similar fashion. This is a standardized way of reporting out the extracolonic findings. You start out with E0. That's a non-diagnostic study. E1 is a normal exam, or anatomical variance. Most of our patients don't have E1s because being around for 50+ odd years, they are usually carrying some sort of simple cysts,

gallstones, renal stones, benign hemangioma, things like that. But there again, these are asymptomatic and so they're not clinically significant. We report them out in the report, but these are E2 findings. E3 findings are incompletely characterized, usually meaning they have to have further evaluation to determine what exactly you're dealing with. And E4s are the bad actors, the solid masses, the aneurysms.

Here's some examples. That is a duplicated IVC on the upper left-hand slide on an asymptomatic individual that came in. Upper right hand is your classic gallstones, renal stones. Lower left hand is your hyper dense nodule in the renal cortex. You can see it on the arrow pointing to it. Now, this could be just a hyper dense cyst; however, it also could be a solid renal nodule. And so that needs to be further evaluated. And then on the right is your bad actor. And this is an asymptomatic patient that presented with a large pancreatic head mass.

Here's examples of the C0 and E0 findings. These are the non-diagnostic findings. With the low dose technique we use a lot of times, we find that internal hardware, orthopedic hardware, produces a significant spray artifact. And you can see upper right-hand slide, that that really degrades looking at the CT image of the pelvis. In the upper left-hand slide is the comparable image within the rectum. That is the manifestation of spray artifact in a 3D modeler. So the spray artifact degrades both the 3D endoluminal model and also the 2D images.

On the bottom left is a spasm. If there basically is synchronous spasm on both the prone and supine run, then that's non-diagnostic because if there's spasm we can't build the 3D model. We can't fly through it. And if there's significant spasm, even the 2Ds you can't see the lumen, and so you would not be able to exclude polyps or masses from that segment.

The nice thing is that this seems to marry up very nicely with optical colonoscopy. Our Achilles heel is the sigmoid colon where we see diverticular disease, muscle hypertrophy. If there's usually going to be a spaced segment down that's collapsed on both views and it's non-diagnostic for us, it's basically the sigmoid colon.

Likewise, the Achilles heel for gastroenterology, it seems, is the very redundant colon, previous surgeries, adhesions, things like that, can't get around the horn. For some reason, at least in our institution, CO_2 always seems to find its way to the right side of the colon. So we hardly ever have a non-diagnostic VC for the right side of the colon, so they marry up very easily. If we fail with the sigmoid, then we can basically refer it over to the gastroenterology department.

And in our institution, flexible sigmoidoscopy is coming back. Because if we clear the right side and we didn't see the sigmoid colon they will basically complete the colon cancer screening with a flex sig, and then basically the patient will be referred in five years for repeat colon cancer screening. Likewise, if they can't get around the horn, like I said we usually

do feel the right side and are able to complete that patient's colon cancer screening.

Reporting of the findings. The CT source data, like all CT data, is stored on the PAC system. The pictorial report can also be exported in to the PAC system, and it is stored with the CT source images. The pictorial report can also be e-mailed to the patient or the PCM, if requested. And we do that at our institution.

We do offer same day reads, as well as routine reads. It's patient preference. The same day read, the CT is read real time. The patient hops off the scanner. We begin reading it. The patient waits for the results. They have a guaranteed follow-on optical for that day. It may not be right after the VC, but it basically is broken up into morning and afternoon schedule. We try and image these guys early in the morning because if we do have a significant finding, we don't want to be dumping on the gastroenterologist late in the afternoon.

Basically, the patient has to fulfill all the requirements for the optical if they're going to do the same day read. They have to be accompanied by a driver and realize that they're going to be there for the majority of the day.

We also provide routine reads, and that's an entirely different standard radiology exam. The patient departs following the study. If there is a significant finding, the patient must re-prep. We schedule these late in the

morning and the afternoon.

All right. The conclusions. Successful CT colonography imaging requires an effective bowel prep with stool and fluid tagging. You have to maximize colon distension. We believe that's best done with a mechanical CO_2 insufflation. You need a multi-detective CT scan. We use the low dose techniques. And then you have to have an effective 3D modeler and radiologists that are trained to interpret the study either using a 3D or a 2D analysis.

This is the Colon Health Initiative, and that's where I work. And any questions?

DR. TALAMINI: Thank you very much.

So this is now the opportunity for Panel members to ask clarifying questions or other questions of these first two presenters for the next little bit. So while the Panel is thinking, I have two potentially trivial questions for Dr. Barlow.

In those patients that had both studies, and you asked them which their preference was, did they also give a reason why they preferred one study versus the other, or was it just a yes/no question?

DR. BARLOW: I think that question was yes/no. Basically the question about those that preferred or preferred VC was basically the convenience of it.

DR. TALAMINI: And this another potentially trivial question.

The size of the catheter that you use to insufflate?

DR. BARLOW: I actually don't know what the size is. I mean I know it's smaller than the standard Bordex tip.

DR. TALAMINI: I think everything's smaller than the Bordex tip.

DR. BARLOW: The Bordex tip, yeah.

DR. TALAMINI: Other questions from Panel members? We can start over here. Yes, ma'am.

DR. CHARABATY: Hi, I'm Dr. Charabaty, gastro at Georgetown.

I have a few questions. So one is how long does it take you to do the VC from the time the patient starts, it's interpreted, and you give the patient the results? And subsequent to that, how many can you do in a day? And then, so -- but my ultimate question is that you have a very organized system in the military, so if you have a positive finding, you send the patient the same day for an optical colonoscopy.

And how do you see this translated in the community where you have busy radiologists that might be giving the results the same day, busy gastroenterologists that have a full colonoscopy schedule, and a patient probably having to come back for optical colonoscopy on another day, you know, so again having somebody to take them home and take another prep, et cetera?

DR. BARLOW: Okay. First, imaging for VC, it fits very well in a standard CT imaging day. I mean it takes us 15 minutes to do -- start to finish.

That's get the patient in the gown, get them on the table. The majority of that is getting the colon distended up to the 25 psi. You know, because it takes it very gently up there. Okay? Imaging is seconds with a multi-detective CT scan, but it usually takes about a couple minutes to get them up the steady state, you know? And what we do is we insert the catheter, the patient -- you know, start the CO_2 insufflator.

Our CT techs have certain positions they put the patient in to basically get good flow of the CO_2 around. And then when they finally have so many liters in, they roll them supine, they do a scout film to make sure that they're well distended, and then they zip them, you know, scan them. Then they basically roll them over prone. Usually when they roll them over prone, they lose CO_2 into the small bowel or it comes out around the balloon catheter into the room. So they decompress the colon a little bit.

So then the machine once again like the little engine that can, it just basically keeps on pushing the CO_2, gets them up the steady standard 25 psi, another scout, and then they zip them and do the prone. And so it fits very well the four an hour you can do in a standard CT schedule.

As far as the same day reads go, yes, we offer that, but I can see the same thing in the civilian sector. It just is what you contract for. I mean if a radiology group basically contracts with a gastroenterology group, and they basically say well we want same day type of service -- I don't work in a fee for system, but I can't see where there would not be some sort of

agreement where they can get in the same day reads.

We don't provide same day reads right now for our teleradiology network because we just don't have basically the organization to do it. That's something we're looking into down the line. From start to finish, 15 minutes to scan the patient and they hop off the scanner. For the same day read, and depending on how many we have that day, we're going to try and get to it as soon as we can. It takes a couple minutes to build the model, then it takes me about 15 minutes, okay, to basically fly the model, look at the pathology, generate the pictorial report -- because I mean you basically have to cut and paste -- and then dictate it out.

We have a redundancy and we have to dictate into our CACS system, so we have double kill there with the pictorial report, but then also the oral dictation. But it takes me about 10 or 15 minutes to get done with that study.

DR. CHARABATY: So how many patients can you screen in a day?

DR. BARLOW: Well, basically -- I mean there again, if we had dedicated -- if you had four an hour, okay, I mean you could do 32. We don't do 32. I can't even fill a CT scanner up, you know. That's one of the reasons why we went to teleradiology because I had here a program that even though we go out and we visit all our branch clinics and we hit the streets and we basically educate our PCMs that this is an option, a viable option, I still can

only get maybe five, seven out of the national capital area, which is huge. Okay?

And so, in order to get the numbers I'm getting, I had to go outside of the national capital area. And the military afforded me -- or the Colon Health Initiative -- the ability to go out and reach these smaller MTFs that were screening. I mean, you know, some of our smaller hospitals don't even have gastroenterologists there, you know. Or the general surgeon and the gastroenterologist there can't handle all of the screening needs. And so, the military was bleeding out to the network, so to speak. They were sending patients out to the network. And so, the COs of those hospitals were saying how is there -- how can we keep basically the military patients in the MTF and screen them?

And it actually was a gastroenterologist, one of our fellows that trained with us who was the first one who went down to Camp Naval Hospital Jacksonville and was in the same situation. Could not meet the screening needs of the community, and the CO is saying, well, what can you do? And he goes, well, I trained up at Bethesda then, it's now Walter Reed, and they have CT colonography. Is there any way that we can have them -- basically, we can acquire the images down here, send them up through a secure VPN link, they build the model, and then send the results down. And that's what we're doing right now. And we're adding on -- because more and more of these smaller MTFs are asking for it.

DR. TALAMINI: Dr. Barlow?

DR. BARLOW: Yeah.

DR. TALAMINI: We got a -- we'll need really crisp answers.

DR. BARLOW: Okay.

DR. TALAMINI: Because we have a huge panel --

DR. BARLOW: Sorry.

DR. TALAMINI: -- and a lot of questions.

DR. CHARABATY: I just have one more question. Just in your experience, because you do a lot of this, as you know, one of the hot topics now in GI is the right-sided serrated cold polyps, the flat polyps that we all worried about missing on colonoscopy because we know that up to 30% of colon cancers come from serrated polyps.

What has been your experience in detecting these types of polyps?

DR. BARLOW: Well, and they're difficult. They are very, very difficult. There are some tools in there that help out a little bit. I didn't talk about the artificial light. You can basically vary the light within the 3D model endoluminally, you know. And, basically, sometimes you can pick up those very, very subtle flat lesions. But, no, they're an Achilles heel to us. We have the same difficulty that a gastroenterologist has in seeing those.

DR. CHARABATY: Thank you

DR. TALAMINI: Dr. Fogel?

DR. FOGEL: Thank you. I have two technical questions. The first is for patients who have had intraoperative -- intraabdominal surgeries, does that affect the sensitivity of your test? Is that because of spray of radiation? Does that alter your ability to detect lesions?

DR. BARLOW: No. I mean if they had intraabdominal procedures, that does leave a lot of hardware. Our problem is metallic hardware, orthopedic hardware, things like that. Harrington rods, bilateral hips, that type of stuff. Prior colon resections, you know, or any other surgery that left little clips, that's not a problem at all.

DR. FOGEL: So in patients who are older, who have had artificial hips, who have had lumbar disc surgery, do you still do those patients, or do you refer them for optical colonoscopy?

DR. BARLOW: No. We still do those patients. Basically, there are ways that you can reduce some of that artifact by changing the windows and levels on the CT scanners. And so, we can get around that by manipulating the image. And we very rarely have C0s. Okay? Or even E0s. I was just giving those as examples where you have to consider that.

DR. FOGEL: My second question has to do with the prep. In Michigan, not all the insurance companies pay for the MoviPrep. What experience do you have with other bowel preps and patient acceptance of these preps?

DR. BARLOW: We used the Fleet's Phospho-soda prior to the

MoviPrep. That was more palatable, but there again, these preps are actually -- we follow the lines of the gastroenterology department. I work for the gastroenterology department. I'm actually an employee of the gastroenterology department, and they set the preps. And at Walter Reed, they moved from the Fleet's Phospho-soda, the phosphate based preps, into the MoviPrep. And I found that -- I had no problems with the Fleet's Phospho-soda for patient tolerance, but I have not had any push back from the MoviPrep either. So the transition didn't cause any push back.

DR. TALAMINI: Dr. Afifi?

DR. AFIFI: I have a two-part question. The reduction in mortality figures that you mentioned, was that colorectal cancer specific mortality and over what period of time?

DR. BARLOW: I didn't --

DR. AFIFI: Okay. Dr. Pignone?

DR. PIGNONE: Yes, those are colorectal cancer mortality reductions. And the ones from the modeling study would have been over the course of the entire 30 years from age 50 to 80. Those are the anticipated ones. From the individual studies, it depended on the length of the study. They were usually about 10 years. Some of them went out to 15, 20 years.

DR. TALAMINI: Dr. Imrey?

DR. IMREY: Dr. Barlow, I'm unfamiliar with the NNMC HEDIS score. And I wonder if you could describe that for me.

DR. BARLOW: Okay. NNMC was National Medical Military Center Bethesda, so that's the old Walter Reed. And, basically, what we did was we took our standard HEDIS scores, which was for the success of your colorectal screening --

DR. IMREY: Well, what is that please? What is that for? Could you interpret that for me?

DR. BARLOW: Basically --

DR. TALAMINI: Can you repeat your question and with the microphone on please?

DR. IMREY: Excuse me. I'm unfamiliar with the standard HEDIS score. I don't know what that means or how it's compiled. Could you interpret that?

DR. BARLOW: Okay. As the way I understand it, it's the percentage of your population that fills the metrics for colon cancer screening. Those that should be screened on your area that 's the denominator, and the numerator is the number that have been screened. Okay? So it's a percentage of those that are fulfilling the appropriate criteria for colon cancer screening.

DR. IMREY: Thank you.

DR. TALAMINI: Dr. Dauer, I think you had a question?

DR. DAUER: Yes, thank you, for Dr. Barlow. Do you have any radiation dosimetry to record or measure the radiation dose to the patient?

And also in your experience, have you ever experienced a perforation from CTC? I know it's rare, but have you ever had one?

DR. BARLOW: Okay. The second question first. Yes, we have had two perforations in the entire time that we've been doing VCs. All of them happened at Walter Reed. None of them happened at the remote sites. They both were patients that basically were totally asymptomatic. They had a history of diverticular disease, but no recent flare-ups of diverticulitis because we do check that before we image them. And, basically, we popped a polyp -- I mean a diverticulum. We basically popped a diverticulum.

And one of them had an uncomplicated -- they came into the hospital for evaluation -- it was one male, one female. The male came in for evaluation and basically left a couple days later without a problem. The female had continued leak of air into the abdomen and had to undergo an exploratory. And they found the perforation and then basically did a segmental resection and a reanastomosis.

DR. TALAMINI: So, Dr. Barlow, were those two perforations with your current insufflation method with CO_2 and the gentle pump or --

DR. BARLOW: Yes. Yes, they were. They were both with the CO_2 gentle pump.

DR. TALAMINI: And that's -- what's the denominator? It's 2 over 15,000?

DR. BARLOW: Yeah, um-hum.

DR. BAUER: Dosimetry.

DR. BARLOW: What's that?

DR DAUER: Dosimetry.

DR. BARLOW: Dosimetry. Yeah, we basically -- we can calculate it. We go back and get the DPL, the dose of product, and then we can calculate what that absorbed dose is. I don't report that out in the reports. Okay? But it is given to me by the CT tech. It's on the bottom of each one of our studies.

DR. TALAMINI: Dr. Ahlgren?

DR. AHLGREN: For Dr. Barlow. It sounds like a bit over 10% of your patients went on to optical colonoscopy. Was that a full colonoscopy, or did they just look for the lesions that were seen? And if it was a full colonoscopy, were you able to capture any data on the number of polyps seen on optical colonoscopy that were not seen on CTC?

DR. BARLOW: It was a full optical colonoscopy. Okay? And capturing the data on the number of smaller lesions found, we didn't capture that. We don't have that.

DR. TALAMINI: Dr. Steinberg?

DR. STEINBERG: I have a couple of questions for both speakers. So I wanted to clarify that what percentage of subjects, patients, are referring for a colonoscopy after a CTC, given the fact that you're finding polyps there? And some of them are false positives too.

DR. BARLOW: Um-hum.

DR. STEINBERG: So is it 10%?

DR. BARLOW: Yeah, it's 10%, yeah.

DR. STEINBERG: And is that -- have you broken that down by age? For instance, patients over a certain age are going to have more polyps than others.

DR. BARLOW: I don't have that -- I mean we could go back and look at it, but I don't have that information, no.

DR. STEINBERG: Okay. And how -- what percentage of your studies are C0s, are inadequate studies?

DR. BARLOW: To give you a -- we have about one or two a month that are C0s. Okay? And there again, that is usually due to spasm. Okay? Incomplete visualization of the same segment of colon because of spasm. It's not due to prep. They're usually very, very clean. And so it basically is due to spasm.

DR. STEINBERG: Okay. I have a question for Dr. Pignone. If I understood your slide correctly, FITs, the fecal immunochemistry test is as good as a colonoscopy, the data shows, in terms of reducing the incidence of colon cancer and reducing mortality. If I understood that correctly, why didn't your U.S. Preventive Task Force say -- I mean given how simple it is and I know we're not supposed to think of cost, but cost is a factor -- why shouldn't that be the best test?

DR. PIGNONE: Well, first of all, the data that you're talking about is from modeling studies, and it is modeled on what you would get if people adhered to the test. So, first of all, you know, you can't -- adherence to two or three colonoscopies is not the same as adherence to 15 or 20 fecal immunochemical tests. So I think -- again, the modeling studies would say that if used at the appropriate interval, you would expect similar results between colonoscopy and fecal immunochemical testing in terms of mortality reduction and incidence reduction, maybe, again, with some error around those estimates. But you still have to translate that into the real world, and adherence is going to be a little bit more complicated for the fecal immunochemical testing, which is one of the recommended potential testing strategies for all the sets of guidelines. Bernard will talk about that later.

Now, again, the trials of fecal occult blood testing were done with guiaic-based tests. I don't think there's any reason to expect that the newer FITs would perform differently, but some people might want more rigorous evidence than that. They're certainly as -- more accurate than the earlier guiaic-based FOBTs.

DR. TALAMINI: Dr. Isaacs?

DR. ISAACS: This is for Dr. Barlow. Your group clearly has a large experience in reading these studies. How would you expect this to translate in terms of sensitivity/specificity out into the community, the community radiologist who may not have the same 15,000 or so cases?

DR. BARLOW: Well, I mean along those same lines, I'm becoming more and more an advocate also of teleradiology. I mean you're right. There is a learning curve with this. And so, you have these centers of excellence that are basically -- you know, have a lot of experience underneath their belt. With teleradiology, basically you can provide peer review. Say there's a remote group that wants double reads and things like that. I mean there are courses out there where a young group that wants to start providing this could go get training, and then they could also fall back upon some of the more established centers to do peer review and things like that.

So I think there's a mechanism for those groups that want to get into VC screening to basically get the training, and then also the support they need to basically gear up and then feel comfortable interpreting those things. And that's my own impression on how you could use teleradiology to help implement that and get the training and the experience up. And if a group doesn't want to -- just wants to provide the service and then have the read elsewhere, I mean there's a lot of efficacy to that too. And then they may want to do that along the same lines.

DR. TALAMINI: Dr. Foxx-Orenstein?

DR. FOXX-ORENSTEIN: Thank you. This is for Dr. Barlow. You do have a very large experience and CAT scans are commonly used. Are you aware or do you identify the amount of dose that patients are getting, dosimetry over time?

DR. BARLOW: We do not report that in the report, no.

DR. FOXX-ORENSTEIN: So physicians that are referring patients, might they keep track of the dosimetry?

DR. BARLOW: They can get it. I mean if they're interested in it, they can -- we can get it, and we can basically calculate the absorbed dose from the CT scanning parameters. But we don't put that out in the report, and I've not had any referring physicians come in and ask for that.

DR. TALAMINI: Yes, Dr. Charabaty?

DR. CHARABATY: I have one question for Dr. Pignone. You showed very nice slides about the disparity between states and people adhering to screening colonoscopy whatever the method that would be. And Dr. Barlow just was telling us how despite the validity of the virtual colonoscopy and him going to physicians and telling them this is available, that even that is not -- his radiology rooms are underused.

So do you expect that adding one more potential screening test would help areas that are underscreened, or it's just going to make areas that are -- or populations or states where already screening is established and well just benefit those populations? Because the whole point is that are we adding more tests so that we can make home cancer screening more available to more people? But it seems to me that even with flex sig and FIT and colonoscopy and virtual colonoscopy, it's the same places are benefiting and others are not.

DR. PIGNONE: I think that's a really excellent question, and thank you for bringing that up. We don't know the answer. You know, certainly the hope is is that if you have different options for screening, that certain features of those options will appeal to certain parts of the population. And so, you would expect that the total percentage of people who would find an option that worked for them would go up. But that has not been, I think, definitively proven.

The one thing I'd say about the preference data is you have to be a little bit careful about asking about preference after the test. You know, I don't think the definitive study about preferences has been done. We've done some small studies where we -- again, before people have had any test, described to them the features of the different tests. And what you see is that people pick different things. No one test dominates. There's no one test that's chosen by 70 or 80% of the people.

And we also know from pretty good prior studies that doctors are not real good at predicting in advance what individual patients would want. So you can't really just say, hey, you came through the door. I know you want a colonoscopy or a CTC. So you really have to ask and describe the information to people, and you'll get a variety of responses. But thanks, that's a really good question.

DR. CHARABATY: And I think just to make more of your point is that some people's preference changes after they got the test. I think we all

have in our practice people going through a colonoscopy for the first time, and after that they say, oh, that was not that bad. Actually it was easy.

DR. PIGNONE: Certainly. I think for all the tests -- and some of the information that Dr. Barlow was presenting I think alludes to that. I mean you learn things after you have the test. It's different than what you were described to before the test. But there's also some element of you experience what you've experienced, and somebody else might have a different experience with that test or with a different test.

DR. CHARABATY: Thank you.

DR. PIGNONE: And I guess I just -- the other thing I'd just say in that regard is that the -- it's not so much -- the data isn't about adherence. The data is about completion of colorectal cancer screening. Many of the people who aren't -- who have not had screening have never been offered screening still. So we still have some work to do in that regard.

DR. TALAMINI: Dr. Zhou?

DR. ZHOU: This is for Dr. Barlow. You have your approval, and you actually gave information about extracolonic findings with this E0 to E4 form. In your experience what are the false positive rate -- let's say you found something, but it turned out is not the case.

DR. BARLOW: I don't have that data. I can't answer that question.

DR. ZHOU: Okay. You really have two reports. One is the C4,

and then one's the E4. So it would be very interesting to see what additional benefit you get by giving the extracolonic findings. But if you have too much false positive rate, that gives a lot of the pressure to the patients.

DR. BARLOW: No, that's true.

DR. TALAMINI: Dr. Steinberg, another question?

DR. STEINBERG: I just want to add a comment. In terms of patient preference and patient choosing, it also has a lot to do with who the doctor is or the person is explaining the different choices. And so, people will choose based on the way the data is presented to them.

But I have a question for you about fecal tagging. Obviously a better test or an easier test would be one in which there's no bowel prep needed. And I know there are reports out there where that is the case. Is there a future that you see without having to give a bowel prep to a patient?

DR. BARLOW: I would love to be able to say yes. I mean I hope that goes away. What I've seen of the studies out there right now, that's a very hard test to read. Okay? And in my opinion, I don't think it's ready for prime time yet. Okay? And so, we're stuck with having to do the bowel prep until we can get to the prepless studies. But there again, you got to remember -- and this is the same bowel prep that they're going to do for a colonoscopy. You just add the other two -- the two contrast agents.

I understand the prep is convoluted, and you're right. You basically have to have a good support staff that explains to the patient why

they're going to take this convoluted prep and then why they need to adhere to it. And so, the prep issues we deal with right now, the support staff, the schedulers, they basically explain to the patient why they've got to take these three agents. And we have very, very good compliance with our patients in taking the prep, and they don't seem to mind it that much, you know.

DR. TALAMINI: Dr. Nostrant, did you have a question?

DR. NOSTRANT: You're talking now about asymptomatic, not previously screened patients. What percentage of the patients are you actually repeating the CTC after polyps have been found and removed? Or are you not doing that at all?

DR. BARLOW: Well, no, basically if they -- at least our institution, if they've had a colonoscopy and basically they're cleared, then it's whatever the histologies are and the follow-ups. So they enter into the colonoscopy arm and the gastroenterologists arm if we find a polyp. We're just screening. Okay? Now, if they -- if they're negative, okay, if they're negative, then we recommend a five-year follow-up. Okay? And in our institution, again, they have an option. They can go either way.

We present them with these are your colon cancer screening options. And so, if they have a VC and it's negative and they come around for their five-year follow-up and they didn't like the VC, I mean -- our schedulers present them an option. They can go either way.

DR. NOSTRANT: No, no, I wasn't asking that. You've done the

VC; you've found a polyp.

DR. BARLOW: Yeah.

DR. NOSTRANT: You send them for optical --

DR. BARLOW: The polyp's removed, yes.

DR. NOSTRANT: They take the polyp out. It's no question there's an abnormal.

DR. BARLOW: Yeah.

DR. NOSTRANT: Are you now again doing another -- if someone prefers, another CTC again figuring he might be negative this time? Are you doing that?

DR. BARLOW: No, because basically that goes down the gastroenterologist route.

DR. TALAMINI: Dr. Fogel?

DR. FOGEL: Yes, this is a question for Dr. Barlow again. How many readers do you have reading this 15,000 or so virtual colonoscopies, and how do you do quality assurance?

DR. BARLOW: Basically we have two readers, two radiologists on staff with the gastroenterology department. And basically they're the ones that are reading the studies at Walter Reed. And so, it's a peer review back and forth.

DR. TALAMINI: Dr. Afifi?

DR. AFIFI: Just to clarify in my own mind, being a non-clinician,

from the patient's point of view in terms of the discomfort associated with the CTC versus the optical colonoscopy, the prep is the same, the bowel prep is the same, and the colonoscopy requires an anesthetic whereas the CTC does not. But then the anesthetic from my own experience is not really all that demanding. So in terms of discomfort, would you say that they are approximately equivalent, the two?

DR. BARLOW: No. Actually the VC is a little bit more uncomfortable than the optical. The optical they got conscious sedation. I mean they're pretty much out. They don't feel any discomfort. Okay.

DR. AFIFI: Right.

DR. BARLOW: With the VC -- and there again, I mean I know I look like I'm 30, but I've had two of them. I had one at 50 and one at 55. Okay? So my own personal experience, you do feel full. When you're up at 25 psi, when your colon is distended at 25 psi, it is full. Okay? Not sharp pain, but a fullness. All right? The nice thing is that basically it's very, very quickly scanned. When we unhook you from the machine, there's a micropore filter at the end of the catheter. You get immediate release of the main pressure that's in there, and then the rest of it, CO_2 absorbs through the colon wall.

You hop off that scanner and go right back to work, unlike the other ones where we're using room air and insufflating with a bulb. They had problems with cramping. They had problems with some severe discomfort.

We had two patients vasovagal in the bathroom after they left. It was very uncomfortable. Well, with the CO_2 mechanical insufflator, I think that's going to revolutionize the whole process, you know.

DR. PIGNONE: I do think it's important to consider the full time period of the patient experience. A not insignificant number of patients with both technologies, colonoscopy and CT colonography, when given surveys after the fact, still have some either discomfort or change in their bowel habits out to about 24 hours. With colonoscopy, a minor percentage of people feel like they can't go back to work the next day even, say 10%, 15%. So while most people do perfectly fine with either procedure, there's a number of people who will be knocked back a little bit either by the sedation or by the prep that will affect them longer than just the time it takes to have the procedure itself.

DR. TALAMINI: Dr. Pinsky?

DR. PINSKY: Yeah, I had a question about -- to Dr. Barlow about the sub-6 mm polyps. So if they only have sub-6 mm, you don't report that to the patient, but is it recorded anywhere for -- in terms of future images to see what the history was? And then, also if you have a 6 mm+ and you are referred to optical, do you tell the gastroenterologist about the sub-6 so they can look for it where --

DR. BARLOW: No, we do not report out sub-6 because the -- basically when you're sending it down to that level, I mean my -- being able to

discriminate between stool and otherwise the resolution just isn't there. So we don't report out sub-6. We do retain the DICON data. We can always rebuild the model back. And we've done that before where we report out polyps, and if the gastroenterologist goes in and finds multiple other polyps, then we can go back and see whether they were gettable or not. And so, we always have the ability to go back and look, but we don't report them out. And so they're still in the record with that model, but we only report out intermediate size or 6 and greater.

DR. PINSKY: Just one follow-up. I mean how accurate is your size measurement in terms of 6 versus 5 when you're measuring to see if it is a 6?

DR. BARLOW: There again, we use the standard. You're supposed to get directly over the polyp with the backdrop of the wall, and then it's the longest dimension and then perpendicular to it. Now, we have CAD coming down the road, which basically hopefully has volumetric assessment based upon density. And, hopefully, down the line that will take away any inter-observer variance in measuring. Yes, I mean you basically -- whenever you got two individuals putting mechanical measurement -- electronical measurement on a bump or a nodule or a polyp, there will be some variance in their measurement.

DR. TALAMINI: Dr. Nostrant?

DR. NOSTRANT: A quick question. There are 15,000 people

that you've done. How long is it -- from what time to what time? How long was it?

DR. BARLOW: 2004 to the present day.

DR. NOSTRANT: Thank you.

DR. TALAMINI: Dr. Charabaty?

DR. CHARABATY: You got it right this time.

All right. I have a question for Dr. Barlow or Dr. Pignone. You talked a little bit about the extracolonic findings, and you showed us like significant ones, pancreatic cancer. But how many of the extracolonic findings were non-significant and would add more cost and more testing? A little pancreatic cyst or, you know, soft tissue that we can't determine and all the anxiety that comes with that?

DR. BARLOW: Well, the 10%, 9%, those we referred on to extra imaging. I don't have the breakdown of how many of them were hyperdense cysts. You have a hyperdense lesion in the kidney, and you don't know whether that's solid or it is a hyperdense cyst, and so you have to do a further evaluation. And so, the percentage of patients going on to extracolonic findings is about 10%. That's what we're seeing. I mean extra imaging. I don't have the costs for that because there again I practice in a -- like in a cost-free environment. I mean we just send them down the road.

DR. CHARABATY: Dr. Pignone, do you have a comment on the cost?

DR. PIGNONE: Although we're, we're not --

DR. CHARABATY: Not -- okay.

DR. PIGNONE: -- specifically considering the cost --

DR. BARLOW: Not so much on the cost. It's just it's been very hard, very challenging to determine how to weigh up the extracolonic findings. Is it benefit? Is it harm? It's probably some benefit and some harm. Some of that harm is resource utilization that ends up not helping the patient, but some of it's also the potential for downstream complications of procedures that follow the initial procedure as well.

DR. CHARABATY: And one more question for Dr. Barlow. Somebody mentioned false positive, when you have false positive on virtual colonoscopy. And so, you send the patient for optical colonoscopy, and the colonoscopy goes back and forth to the cecum fives times and tells you I can't find it. How is this addressed or followed up? Do you repeat a virtual colonoscopy after a short interval? Do you repeat a colonoscopy after a short interval? How is this managed?

DR. BARLOW: The first thing -- I mean if we call something in the colon and the gastroenterologist can't find it, okay, we'll get a call, and basically we'll come back and pull the study and review it. Okay? And, basically, look -- then he or she will ask us, what is your confidence interval? How positive are you on this? If we are positive or very extremely positive, i.e., we can see it on the 3D, the 2D, it's got the right attenuation, then we'll

tell him or her that, oh yeah, we have a high index of suspicion. If so, then they will do a short interval VC to follow up on it. Okay?

If, however, it comes back and we're looking at it and reviewing it and the gastroenterologist says, look, we didn't find anything there. I mean there's nothing, clean. And then we go back and we say, okay, well, basically could have this have been some stool or something along those -- and we'll reevaluate our call on that case. And so, that's another indication where you got good interface between your gastroenterologists, good to and fro back, and you get to basically tune up your scanning pattern and your criteria on what you call.

So we do interact with them whenever we have a discordant colonoscopy VC. And we do problem solve, go back to the images, and solve it that way.

DR. CHARABATY: Thank you.

DR. TALAMINI: Dr. Imrey?

DR. IMREY: I'd like to return very briefly to the compliance scores that were shown by Dr. Barlow for a recent paper this year. I wonder if you or Dr. Pignone, or for that matter anybody here, has information on how those data were obtained. What conditions -- were those trial data? Were those a screening offering comparison or purely observational? Could somebody clarify that?

DR. CHARABATY: You're talking about the HEDIS now?

DR. IMREY: Yean, the HEDIS scores.

DR. PIGNONE: Yes, those scores are just simply a percentage of people who are up to date for screening by any of the modalities in a given population.

DR. IMREY: But there are two rows given: one with and without CTC. And I was wondering what the distinction between those groups was.

DR. BARLOW: Yeah, basically what it is is --- there again, VC is not recognized as a HEDIS metric. You can't include them in that score. So the top score is what we were doing -- our metrics for colon cancer screening just based upon what was out there. That was the BE, the fecal occult, that was the opticals. Okay? And that was just -- then the bottom row is just -- okay, let's just play devil's advocate and throw in the VCs because once they've had a VC, then they've been screened for colon cancer. And so, you can take the number of patients that we were screening, throw them into the mix, and see what happens to the HEDIS percentages.

DR. IMREY: So just to clarify, so that's simply an accounting distinction, not a distinction between groups that received different offering patterns or restructures of --

DR. BARLOW: No. It's just a numbers crunch.

DR. IMREY: Thank you.

DR. TALAMINI: Dr. Kelsen?

Speak more directly into the mic, please.

DR. KELSEN: Okay.

DR. TALAMINI: Thanks.

DR. KELSEN: Sorry. This is for Dr. Pignone. If I understand this correctly, fecal occult blood using a FIT approach, if you did it every year for 20 years or something would be possibly competitive with colonoscopy q5 to 10 years. The difficulty is compliance.

Is there modern data on using that approach in which the primary care physician or nurse practitioner or somebody does the same test when the patient is in their office where you don't have this issue of sending a card home and compliance, et cetera?

DR. PIGNONE: You know, up until recently there's a lot of focus on discouraging in-office testing because the technologies were pretty clearly ineffective when used on an in-office exam. There are now some of the fecal immunochemical tests that are really one-time samples. And so, while we would still not recommend that the test be done on a digital rectal exam sample, it's conceivable that someone could come to the office, have a bowel movement, have an FIT test done, and that would be as good as a home sample for the single testing.

It's not clear that the single FIT test performs as well as the two or three sample. And, of course, with each of those tests you can set your threshold for positivity in terms of the reactivity of the test at different levels.

It's actually quite complex. That's one of the things -- not every FIT is the same as every other FIT, and what is the threshold for deciding which ones are in or out, I think, is a tough question that you guys maybe need to take on in a different forum.

DR. KELSEN: So I take it that the data actually doesn't currently exist using an optimal fecal occult test of any type done under office circumstances for the compliance issue?

DR. PIGNONE: Not to my knowledge. Certainly not the point of correlating it with outcomes. You know, you really just get accuracy data, and it would be one time accuracy data. The other problem is is that we don't have good longitudinal -- or only limited data on longitudinal data studies of adherence and what the adherence patterns are like. If you do the first two or three, are you likely to do the next five versus is it more random? And those are important distinctions that affect the modeling results.

DR. TALAMINI: Dr. Jiang?

DR. JIANG: A question for Dr. Barlow. So the extracolonic cancers that you found, are those for patients that first time come for VC? Or do you have information on that?

DR. BARLOW: Yeah, these were first time screening patients.

DR. JIANG: So do you keep track of a patient coming back?

DR. BARLOW: Yeah, we have -- our nurses follow all of those calls all the way to the soft tissue diagnosis, if that's what you mean. I mean

if we have identified someone with an extracolonic cancer, basically then they will follow that patient -- they will get access to the medical record, and they will follow the patient to whatever the resolution is. Usually pathology.

DR. JIANG: So, I'm wondering if the patient comes in for a VC and then five years later comes in for another VC, do you have the information on -- is the first time around or the second time around -- and do you refer back to the first one?

DR. BARLOW: Yeah, we do. Basically, we have all of the patient's prior ultrasounds, CTs, MRs, everything they've had in their file. And when they come back for a follow on -- five-year follow-up, let's say, we go back and compare the original VC. So we have that in our PAC system. And the thing that surprises me is from a radiology standpoint, I've always been used to the paradigm that no one reaches 50 without having been imaged multiple times: ultrasounds, CTs, MRs, and everything like that. But my paradigm is the patient's already got pathology and we're sequentially following him.

I am surprised at the number of colon cancer screening patients that are showing up -- this is the first cross-sectional study they have ever had. The women have had mammograms, the gentlemen have had chest x-rays, maybe an ankle here or a foot there, but I mean really this is the first cross-sectional imaging study that they've ever had.

DR. TALAMINI: Dr. Steinberg?

DR. STEINBERG: You may have said this and I missed it. How long does it take you or your average radiologist who reads these to read a virtual colonoscopy?

DR. BARLOW: Ten to 15 minutes. But that's start to finish. That's generating a pictorial report and then dictating out the study, which, there again, may be a little overkill.

DR. STEINBERG: That sounds a lot faster than I thought.

DR. BARLOW: Well, I mean there again it also depends upon how many you've done. When we first started out, it was taking me 30, 40 minutes to read. Okay? But then also with the dual synchronized fly-through, the way we read them, I only fly up the colon once in the supine run and then come back to prone because I'm looking at both of them as I fly up and as I fly back. That cuts the read time down in half. And so, then it's just up and back and then read the CT scans, both prone and supine, read the two scout images -- because you're responsible for the whole package -- and then get the report out and -- I think we do a good job at 15.

DR. TALAMINI: Dr. Lurie?

DR. LURIE: Yeah, I think it's a question for Dr. Barlow. With respect to the C0 studies or inadequate -- your inadequate studies, do you have a sense that -- from randomized controlled data or other -- just from your own experience, whether there might be studies that would be considered inadequate preps for an optical colonoscopy that you might be

able to do with a CT colonography?

DR. BARLOW: I didn't understand the question. Say that again?

DR. LURIE: So the question is are there times that there might be a prep that is inadequate for optical colonoscopy but you would have been able to scan that patient successfully?

DR. BARLOW: We do. We will take the failed OCs from the GI department. And occasionally they are basically just too much stool, too much liquid stool. What we do is then we give them the two contrast agents, the Gastroview and the barium enema. We wait two hours for the contrast agents to reach the colon. Meanwhile, they're using the bathroom too and hopefully clearing as much as they can out of the colon. But we have found that with the tagging, we can get a very good study of the colon. And so, we have done some failed opticals for prep issues. We've been able to do the study.

DR. LURIE: Okay. So there's always some degree of re-prep? In other words, it's not as if you take them from the one suite into the other and --

DR. BARLOW: No, no, no, no.

DR. LURIE: No?

DR. BARLOW: No. We have to have the stool and the fluid tagging --

DR. LURIE: Tagged, right.

DR. BARLOW: -- to clean that out. We cannot see the wall. And there again, there are even problems with -- I mean if there's too much fluid on board and we give them the agents then -- both contrast agents, and they get diluted out to a point then it's below the cutoff level for the electronic subtraction. And then the -- view is the distended colon in the prone and supine. Because if that fluid gets too dilute that it won't be subtracted out, then what you do is you've got a lake on the dependent portion of the colon you're flying through.

And so basically what happens when you do prone and supine and you throw that fluid, that non-subtractable fluid to another segment of the colon, that's how you then piece the two together and get an adequate diagnostic study.

DR. TALAMINI: We have two minutes for one last question.

Dr. Dauer?

DR. DAUER: Just to clarify, when you said you look at two views at a time, do you do the prone and supine fly-through, or do you it 2D and a 3D together?

DR. BARLOW: No. We do a 3D --

DR. TALAMINI: Into the microphone please. Thank you.

DR. BARLOW: Okay. We do a 3D synchronized fly-through. So in other words, I've got four panels when I'm looking at it. I've got the supine

run, the prone run, 3D endoluminal, and then I've got the 2D above. And the 3Ds are synchronized so we're flying through the same segment of colon. And there again, this has been possible because of that CO_2 insufflator. I mean my hat goes off to Perry Pickhardt and their original trial. If you looked at that, there was a lot of segments there because the patient was doing a lot of spasm. Okay?

With us, the rule rather than the exception is you can fly through a long segment of colon because it's nicely distended. Single run all the way through. And so, basically when you do that, you can see artifacts or abnormalities on the wall coming at you. And so, then you do a quick crosscheck over to the contralateral view, the prone view, and if there's nothing there, that is an artifact. That is stool, that is fluid, that's subtraction. You don't even need to stop; you don't even need to stop and interrogate it or use your other tools. You can just fly straight on through.

So the idea of having a synchronous fly-through model helps us and reduces read times, at least for our institution.

DR. TALAMINI: So I want to thank our speakers for clear presentations and great answers. Thank the Panel for great questions. We will now take a short 15-minute break.

Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any member of the audience.

We will resume at 10:00 sharp. Thank you.

(Off the record.)

(On the record.)

DR. TALAMINI: We will reconvene. Panel members please take your seats. Okay.

This Panel meeting is now back in session. The time is 10:00. And we will ask Dr. Perry Pickhardt, Professor of Radiology, Chief of Gastrointestinal Imaging, University of Wisconsin-Madison, for our next presentation.

Dr. Pickhardt.

DR. PICKHARDT: Thank you and good morning, and I'd like to thank the Panel for this opportunity.

I'll be limiting most of my discussions specifically to the Department of Defense CT colonography trial, which was conducted now over a decade ago. I was stationed at the National Naval Medical Center in Bethesda from 2000 to 2003, and in that time we were able to organize, conduct, and publish that trial. And I've been at the University of Wisconsin since that time in late 2003.

These are my disclosures, some of which may not have much relevance. Others are more related.

In terms of the DOD screening trial, this was a prospective validation trial. And so, at the time that this was first -- at its inception around 2001-2002, CTC at that point had yet to be proven in the screening

setting. There was really no data.

This was a trial of three military medical centers: the National Naval Medical Center where I was in Bethesda, the Walter Reed Army Medical Center -- since that time those two have recently merged, as you may know -- and then the San Diego Naval Medical Center was the third arm.

The funding was provided through the Department of Defense, and this was through Advances in Medical Practices. There was congressional funding.

There are many publications that came from the data from this trial. I'm going to focus really on the main results, but will briefly mention a couple of other articles. And I know Dr. Summers will be able to touch perhaps on some of the other data as well. And this is the paper that I'll spend most of my time discussing.

The primary goal of the trial overall was really to assess the performance characteristics of CT colonography in an average risk screening cohort. And our reference standard was same-day optical colonoscopy with the use of segment and blinding, which I'll talk about in a moment.

In terms of methodology, all patients underwent same-day CT colonography and optical colonoscopy, similar to how we do this in clinical practice in our screening program, at least for those that are positive now. Obviously all patients underwent both exams in this screening trial.

In terms of including criteria, it was strictly the criterion of

asymptomatic adults eligible for colorectal cancer screening according to the major guidelines, but there are many exclusions, and they're listed here. This is straight out from the paper. Any symptoms really that could be referable to a possible cancer -- bleeding, iron deficiency anemia, unintentional weight loss, all these folks were excluded. If you had screening within a period of time, that would make you not eligible. If you had inflammatory bowel disease, history of adenomatous polyps, cancer, so and so forth, family history of hereditary cancer syndromes and so forth, or simply couldn't undergo the prep we were using, those were all excluded.

The bowel prep is somewhat similar to what Dr. Barlow had indicated. At that time we were using phospho-soda prep, but the oral contrast tagging portion is similar to what we are still using now, although the volume has been cut in half in our current clinical practice. And we're now using magnesium citrate, which is really as good, possibly better, than phospho-soda and theoretically safer.

Colonic distension at that time, as was mentioned, also was room air insufflation. This is using a barium handheld bulb, the blue bulb if you will. And this is generally self-administered by patients to tolerance. If they weren't comfortable doing that, the technologist would provide the puffs, if you will. But as I'll mention later, this is one of the drawbacks of our methodology compared to how we're doing CTC today.

In terms of CT technology, this is also relatively old technology.

They were four detector and eight detector row scanners, which at the time was really the current state of the art. This was relatively low dose scanning, certainly compared to diagnostic CT, but of course we've dropped the dose considerably further since the time of this trial as well.

We only did supine and prone scans, so if there were cases of inadequate distension, we had no way to really remedy that by performing a decubitus view to try to salvage the exam. We simply had to read what we had.

The interpretation was on a dedicated virtual colonoscopy software system. There were six board-certified general radiologists. I believe one of them have had fellowship training in abdominal imaging. We had no formal training. It really didn't exist at that time. And at most we had informal experience of 25 to 100 cases, so a fairly inexperienced group in terms of the start of the trial. By the end of the trial, we obviously had more experience.

We used a primary 3D fly-through for initial detection using 2D, of course, for detection and confirmation as well. And 2D images are used for the extracolonic evaluation. This is the system similar -- Dr. Barlow is also using this system. And, basically, the 3D fly-through is what's used for most primary detection with 2D to always confirm. And so, you've seen that.

In terms of optical colonoscopy there are -- this was done immediately after CTC interpretation, usually within a matter of an hour or

two from the time of interpretation. Conscious sedation and pain control was, of course, used. And segmental and blinding really provided an enhanced reference standard because we were able to not only assess CTC, but we could also provide some assessment of colonoscopy.

Because as an endoscopist pulled out of a segment -- that is the way endoscopy is performed. They made it to the cecum to the right colon, and as they pulled out to the hepatic flexure, the nurse or study coordinator would then unblind the CTC results. If there was a finding -- at CTC there was 5 mm or greater that was not seen at colonoscopy on the first attempt, they would go back and reexamine that area to see if there was -- if they could find their own miss essentially. And that does provide some enhanced reference standard.

Of course, there are cases now in our clinical experience where we won't know if it's a false negative until a subsequent future study, but this does provide at least some improved reference standard. And, of course, all polyps that were retrieved were sent for histology. We recorded room times, and that was really entire total time of the patient in the CTC suite or endoscopy suite.

The matching algorithm was pretty straightforward. A lesion was considered a match if it was in the same or adjacent segment on the two studies. We used the flexure as a segment so that actually made it a little more difficult to match some lesions that were probably true matches. Size

was -- had to be within a 50% error margin. And, in general, because of the low prevalence of significant polyps, especially those 1 cm or greater, matching is generally quite straightforward with a few exceptions, of course.

We looked at by patient and by polyp performance characteristics, specifically with CTC. I'll talk about sensitivity and specificity by size threshold at 6 mm and above. And then we can also look at sensitivity for colonoscopy prior to the unblinding of the CTC results.

So getting to the results, first of all, the cohort was 1233 asymptomatic adults, typical screening population of about 58 years on average. A fairly even gender mix, slight male predominance. There were 20 subjects that were excluded either for incomplete colonoscopy, inadequate prep at colonoscopy, or mechanic failure, including perhaps the CT scanner failure.

There were a total of over 1300 polyps, so slightly over half of all patients had at least one polyp. But as you'll see, the vast majority of those are diminutive lesions. Almost a thousand of those were 5 mm and less and of doubtful clinical significance. Those of potential significance, 6 mm and greater, there were 344. And of those, 210 were proved to be adenomatous at the 6 mm threshold, 51 of which were 10 mm or greater or 1 cm or greater. The adenoma prevalence was 14% of the 6 mm threshold and 4% of the 10 mm, and that's very similar to other experiences of both colonoscopy and CTC since the time of this trial, including our experience at

UW.

There were 59 advance neoplasms, including two cancers. And I'd point out that was about what we expected. We anticipated about one asymptomatic unsuspected cancer in a true screening cohort every 500 patients, so that was about what we were anticipating. Advanced neoplasms included advanced adenomas, so large adenomas over a centimeter or those that have histology of significant villous component, like a tubulovillous adenoma or villous adenoma, or hybrid dysplasia are also included if they are under a centimeter.

The results -- this is right from the paper, and obviously I don't expect you to try to digest all this information. But the next slide will kind of boil it down to the results at the 6, 8, and 10 mm thresholds. So CTC sensitivity -- these are by patient results for adenomas. And you can see at 8 mm, CTC sensitivity pretty much plateaued and stayed above about 93, 94% at 8 and 10 mms, similar to optical colonoscopy sensitivity, slightly greater at those higher -- at the larger thresholds. But you can see they switch, and CTC is slightly less sensitive at the 6 mm threshold compared to colonoscopy. And those are not statistically significantly different.

Specificity was quite -- was only 80% at the 6 mm threshold, and I'll get into reasons, potential reasons why, but at 8 mm the specificity was over 90% and increased to 96% at the 10 mm threshold.

In terms of advanced neoplasms -- and this is really the primary

target of colorectal cancer screening in my opinion. And some others would be to detect and remove all advanced neoplasms, as I previously defined. And, of course, invasive cancer is important, although we only had two of those. Not much of an endpoint. You can see CTC sensitivity for advanced neoplasms is comparable to optical colonoscopy, about 90% for reach. Both cancers were detected at CTC prospectively, and one of the cancers was found only after segmental and blinding at colonoscopy. That was a right-sided lesion, where CTC I think has some inherent advantages.

This is just the example right out of the paper. I don't know how well you can see. There's a red dot in the cecum that indicates the location of a polyp that is shown here on 3D and 2D. This is a 16 mm pedunculated polyp in the cecum that proved to be adenomatous at same-day optical colonoscopy and after resection sent for histology. And this is a typical easy case to match up.

In terms of room time, the patients were in the CT suite for about 14 minutes on average. It was a little over twice that for endoscopy at 31 minutes. If you include post-sedation recovery, which we don't have for the CT portion, it was about an hour and a half on average of post-sedation recovery.

There are a lot of other data points that I won't have time to get into. I think Dr. Summers will discuss some of these, including the computer aided detection, patient preference data, extracolonic findings, and

may have time for some other things as well.

I'll briefly mention flat lesions and OC performance, as we've already discussed some of that, but I'll also reserve most of that discussion for Dr. Summers' portion when there's a little more time.

So, in summary, with the DOD trial, our conclusions right from the paper were that CT colonography or virtual colonoscopy with the use of this 3D approach is an accurate screening method for detection of colorectal neoplasia in asymptomatic average risk adults, comparing favorably with optical colonoscopy for detecting clinically relevant lesions.

In terms of strengths of the study, I think ways we improved on prior work at the time was we added the 3D detection, which I think with the right software greatly improves accuracy. We also used the oral contrast tagging, which I think improves both sensitivity and specificity if done appropriately.

Some of the drawbacks though, as we mentioned, we did use the room air technique, which leads to under-distension, probably impacted our performance characteristics somewhat. Also, we did not perform an additional view in those cases of suboptimal distension, so there were cases I'm sure where we probably missed polyps because of under distension.

Electronic cleansing, at the time -- this was older technology and at the time it was very -- it was sort of nascent technology that had not matured, and led l believe to a lot of the false positives down at the 6 mm

threshold. We actually don't use electronic cleansing or digital subtraction and haven't for the past decade. In our experience, our prep leads to very little fluid that's tagged and is easily interpreted on the 2D views and obviously changes orientation on different positioning at 3D.

And then, finally, there's' no real gold reference standard in the sense that some of the cases where now -- there was a question earlier about what do you do when a lesion -- that CTC has not found at colonoscopy. In some of those cases we do exactly -- we read these in consensus clinically now. But some of those cases, we have to make a determination whether CTC needs to be repeated or willing to call it a false positive. I want to say about half of the cases where we repeat the VC, the lesion is found to be a false negative colonoscopy finding. But that's not included in this trial data.

And I would just mention that this trial has been cited over a thousand times in peer-reviewed publications by subsequent works.

Real quickly, looking at location of adenomas missed by optical colonoscopy, what we were able to show by using a separate reference standard that is not just simply doing back-to-back colonoscopies, which any systematic miss -- for example, a polyp behind a fold could be missed by two successive colonoscopies. But with virtual colonoscopy, we were able to show that that misread was probably double what the accepted miss rate of 6% for large adenomas were. And the reason is largely, as I mentioned, behind folds, typically in the right colon.

And as Dr. Barlow had shown, we were able to see with virtual colonoscopy that we can demonstrate these blind spots. As you're going forward in one direction, it appears that you're seeing everything. When you turn back and fly the other way, you see the relative blind spots at endoscopy. And those are, in fact, the location of the majority of adenomas that are missed at endoscopy. So it's a complementary test. There are certainly blind spots for virtual colonoscopy that may get complementary to optical colonoscopy.

Flat lesions. This is a topic that I won't have time to get into in any great detail. We looked at our DOD experience. From that trial, we basically found that the results compared to optical colonoscopy were similar, and we actually felt that this was not a significant drawback to screening as the detection rates were similar to polypoid lesions. They are more -- they're less conspicuous. They're more difficult to detect, but at least relative to optical colonoscopy, our results were comparable. But I don't have time to get into the details of that.

I thought I would just briefly finish with a couple of slides on where this led. This trail directly led to the Colon Health Initiative. Right before I left Bethesda we were able to gain funding for this Initiative, and Dr. Barlow then has told us about the productivity of that program since then. And I went off to the University of Wisconsin where we also started a screening program. And between our two programs, we've each screened

more than 10,000 adults with many publications and grants and so forth.

But the one paper I thought I would mention is our subsequent trial at the University of Wisconsin, which really now looked at the clinical impact of CT colonography. This is not a validation trial. It's basically parallel arms of screening with CTC versus colonoscopy. So we looked at our first 3,000+ patients that underwent CTC screening in our program -- and these are asymptomatic adults -- and looked at a similar cohort of consecutive adults undergoing colonoscopies. A very similar age and gender mix.

We sent about 8% of patients on to colonoscopy in our program, and that still holds true. Most of those are for large polyps, but patients can opt for a 6-9 mm polyp being resected at same-day colonoscopy.

And if we look at advanced neoplasms, again, that's -- in my opinion, the primary goal of screening is to target these and remove these. We found similar numbers of advanced neoplasms and actually more cancers in the CTC trial despite the fact that many fewer polypectomies were performed. And this gets back to the point of diminutive polypectomies largely driving up complications and costs without any obvious or immediate benefit. Of course, that's a point of contention depending on your position on that.

We found eight extracolonic cancers in this series at CTC. And I would say we haven't had any complications in our 10,000+ patients at CTC. No hospital admissions; no perforations. In this group alone here, we had

seven perforations at optical colonoscopy, most of which required immediate surgery.

So, in summary, with the *New England Journal,* that UW paper, we concluded that primary CTC and optical colonoscopy are similar in terms of detecting advanced neoplasia, but the number of polypectomies and complications are less for the CTC group. And that provides further support that CTC is an effective primary screening test before a therapeutic colonoscopy.

So if removal of advanced neoplasia is the primary goal of screening, I would submit that in my opinion it is from a cost effectiveness -- and I know we're not concerning ourselves with that -- but clinical efficacy as well, as that's the primary goal. I think CTC has been shown to be at least as effective but results in fewer complications and utilizes fewer resources, as well as detecting extracolonic pathology.

Thank you for your attention.

DR. TALAMINI: Thank you, Dr. Pickhardt.

Are there any very brief clarification questions from the Panel members? Yes, sir?

DR. ZISKIN: One out of two invasive cancers was detected by the CT but not by the direct colonoscopy. Can you say anything about why it wasn't detectable with the direct colonoscopy?

DR. PICKHARDT: Sure. And obviously this is anecdotal. You

know, one out of two is not really of any real significance, but I can tell you in that particular case it was a right-sided lesion, that after talking to the endoscopist, it was near the hepatic flexure. The scope kept slipping past this point. And I'm not an endoscopist, but I've been in a few where I know sometimes you can't evaluate certain segments because of the position of the scope. It kept slipping past the point, and at some point they decided, well, okay, we're just not going to be able to evaluate that segment. When we unblended, the nurse said, no, there was a large polyp there.

And they really did a nice job to continue looking and maybe put pressure on certain area -- there's different techniques they can use -- and were able to finally find that lesion. So it just shows the complementary nature of these two tests. One's a physical test. One's a more virtual test. In the right colon we have the advantage of no physical constraints. We can obviously look behind every fold, which can't be done at endoscopy.

But, for example, in the sigmoid colon where there's diverticular disease, we have a more difficult time. And that's where colonoscopy probably has some benefit on the left side. So I don't want to impugn one test versus another. I think they're both complementary. They both have a very high cancer detection rate, but I think our misses are generally different than their misses, so they tend to be very complementary tests.

DR. TALAMINI: So these have to be very quick clarification

questions and very focused answers. We have two more presentations --

DR. PICKHARDT: Sorry.

DR. TALAMINI: -- before the hour.

So, Dr. Zhou, very quickly.

DR. ZHOU: Just clarification on your University's screening test. Which design -- did you use a paired design, or did you use a two-group design to compare OCT and OC screening?

DR. PICKHARDT: Those were just parallel screening experiences, consecutive experiences. It was not randomized. There wasn't really a controlled study.

DR. ZHOU: Okay. Gotcha.

DR. TALAMINI: Dr. Nostrant?

DR. NOSTRANT: That's a very high perforation rate, so I'm just wondering of those perforations, how many of those were therapeutic perforations and how many were diagnostic, meaning people had polypectomies?

DR. PICKHARDT: Right. I think -- and as I recall, there was about half and half. I think most of them were more traumatic injuries related to abrasion and pressure from trying to get to the right side. That's about 2 per 1,000, and that's within the published rate. But I think it is a little higher than we expected. Just real briefly -- I know. I'll keep this brief, but many of those were not really linked to the colonoscopy. We actually went

and looked at the emergency in these patients and found that they may have come in one or two or three days later presenting with their perforation.

And so, it doesn't -- I think the complication rate of colonoscopy sometimes doesn't always capture those more delayed complications. Many of those were immediate, but some were delayed.

DR. TALAMINI: Dr. Charabaty?

DR. CHARABATY: I just had the same comment because like the national average for perforation is between 1 in 1,000, 1 in 3,000, and I just thought this number was much higher.

DR. PICKHARDT: Right. So this is 2 in 1,000. I mean it's not that much higher. And there certainly are experiences that are higher than that.

DR. TALAMINI: Thank you, Dr. Pickhardt.

Our next speaker will be Dr. Abraham Dachman, Professor of Radiology, Department of Radiology, University of Chicago.

Dr. Dachman.

DR. DACHMAN: Thank you very much for inviting me.

So I was asked to limit this discussion to the so-called ACRIN Trial, National CT Colonography Trial -- Dan Johnson.

These are my disclosures, none of which I think impact significantly in any way.

This is the paper acknowledging Dr. Johnson and all those who

contributed to that titled, "The Accuracy of CT Colonography for Detection of Large Adenomas and Cancers."

The background information -- I'll refer to this as the ACRIN Trial, which is, many of you know, the American College of Radiology Imaging Network. And I will just outline a little bit of the background and spend most of my time summarizing the methods, results, and mention a few other points that followed.

The background is at the same time that the DOD trial that Dr. Pickhardt nicely described was published, at the same there was also an ACRIN retrospective trial. ACRIN had decided to then seek funding for a prospective trial. There was a perceived need to clinically validate the findings of the DOD trial in a large civilian multi-center screening cohort.

Now, the main aim of this paper was to prospectively evaluate the sensitivity of CTC for detecting participants with at least one histologically confirmed large adenoma carcinoma, setting 10 mm as the key metric by using optical colonoscopy as the reference standard.

So the schema for the trial is patient recruitment and patients undergoing CT colonography. At the time -- although now we know that it really doesn't matter whether you read something in 2D and 3D, at the time we weren't sure so we used a randomized to primary 2D or primary 3D reads. And all the patients -- pretty much all the patients had a same day optical colonoscopy -- the prep was adequate for both examinations. And if a polyp

was found, there was a polypectomy, and the polyps were measured at colonoscopy unless they had to be resected piecemeal.

Our consensus lesion matching was done using CTC to optical colonoscopy. Very few patients had some sort of discrepancy that then required consensus, decision-making, and stratification by histology and polyp size. There was a recommendation, not a mandate, but a recommendation for follow-up colonoscopy if there are CTC false positives at the 10 mm or larger level.

So key aspect of the methods. Here we have a larger number of clinical sites compared to previous trials, 15 sites. And very importantly, it included both large and small academic sensors as well as private practice settings. These were asymptomatic patients, 50 years or older, as long as they didn't have a colonoscopy in the five years prior. So the study was conducted between February 2005 and 2006.

I did not put in this slide about prep, but since I believe -- I'm not sure if it was Dr. Fogel had asked about this previously. About 60% of the patients had a polyethylene glycol prep, and about 40% had a saline cathartic prep. And ultimately it really did not make a difference the type of the prep.

You can see the exclusions here are fairly standard. And I do want to point out that the CTC technique, while state of the art at the time, is basically following current recommendations for CTC technique in terms of scanner type, et cetera. All of the patients had glucagon, although now we

do consider that optional, and mechanical carbon dioxide insufflation, as described previously.

There's publications and presentations detailing the radiologist training and testing, so there was radiologist training and testing, as we had known from previous publications that minimum training is required. And now there are published guidelines for that.

Polyp size was defined as the longest dimension as seen on 2D images, and lesions 5 mm and larger were reported. In this case, the same day optical colonoscopy was done without segmental unblinding, unlike the DOD trial, and consensus lesion matching, as I mentioned. Now, the 90-day follow-up OC was recommended, and we'll see that some of the patients had it.

Per the *New England Journal* website, I found that the article was cited about 273 times, as of the last time I checked.

The patients' age and gender of the cohort, you can see over here -- and just to point out a few of the metrics. So when we say here, no cancer or adenoma as opposed to no lesion is 2,249 patients. Therefore, the total number of patients that I'll detail in follow-up slides here are the 2,531 patients. And let's take a look at some of those details.

So of the 2600 patients recruited, there were ultimately 2,531 patients who successfully completed CTC and OC. And although I did not have -- planned this in my presentation, again, because of the question that

was asked previously about the C-RADs scoring criteria, I went back and there was a supplement that did describe one patient in the cohort that had inadequate -- was excluded due to inadequate insufflation. So inadequate insufflation was very rare.

There were 2,141 normal exams, and 390 or 15% of the patients had polyps. And the total number of polyps was 547. So of those, 108 patients or 28% of those were non-adenomas, and 32% of those 173 polyps -- by polyp and by-patient data. The adenomas/neoplasia, meaning for the primary aim of the paper, there were 282 patients or 72% of those who had polyps, and 732 polyps or 68% of those who had polyps were neoplasia.

Now, let's take a look at that primary aim cohort in a little bit more detail. Between the 5 and 10 mm metric, there were 173 patients or 61% of those patients of the 282. And they comprised 239 out of the 374 polyps detected. So 64% of the polyps were in that less than 10 mm range between 5 and 10. 10 and above there were 109 patients representing 4% of the total cohort and 28% of the patients who had polyps. So in all there were 128 polyps, which represented 23% of all the polyps, and of those 7 were frank carcinomas.

So the key metric, which was the by-patient results is shown over here with lesion threshold on the X axis -- so that's not range, it is threshold -- and sensitivity on the Y axis shown for the different ranges. So

the key metrics per the main aim was the 10 mm level, and you can see that the sensitivity at both the 9 and 10 mm threshold was 90%, the specificity was 86%, and in general the larger the lesion, the better the sensitivity. And in terms of follow-up, published guidelines and recommendations, looking at the difference between the 5 and the 6 mm threshold, this is I think what led to the ultimate recommendation the way we read CTC now, setting 6 mm as the threshold for reporting.

The per-patient accuracy for neoplasia is shown here. I just want to focus again on the sensitivity at both the 6 and 10 mm threshold. The 6 mm was 78%. And also, looking at the area under the curve for the ROC curve, which would take into account false positives, at the 10 mm level it was .89, and at the 6 mm level it was .84.

Now, the by-polyp results, which one expects to be not as sensitive as the by-patient data, is shown over here. And you can see at that 6 mm level, they drop to 70% with 270 lesions. And, again, at the 10 mm level, an 84%.

Just to comment on the CTC missed lesions and complications, there was one missed cancer in the rectum, which was not visible in retrospect. There were 30 lesions in 27 patients not detected on CT colonography. And as I mentioned before, there was a recommendation for follow-up. Fifteen of the 27 patients complied and had follow-up with 18 lesions found. So five of those 18 lesions were confirmed on optical

colonoscopy and therefore converted to true positive CTCs. And you could see the details of their size and histology. One patient had severe nausea and vomiting. There were no perforations.

Optical colonoscopy. There were five optical colonoscopy false negative patients on the first optical colonoscopy. One patient had some hematochezia after polypectomy. There's one patient who had a bacteremia, and since both studies were on the same day, it's not attributed to any one study in particular.

So the conclusion from this trial was that the sensitivity certainly increased with polyp size. The specificity remained relatively high across polyp sizes. And the by-patient sensitivity for neoplasia was 90% at the 9 and 10 mm thresholds, with a specificity of 86%. There was a .83 prevalence of lesions -- of adenomas 6 mm and larger, which will impact, of course, the referral rate to optical colonoscopy. Using the 6 mm threshold, it would have been 12.3 referrals -- referral rate to optical colonoscopy. In other words, that would include the false positives. The specificity would have increased to .91% and the sensitivity would decrease to .88% for those large adenomas.

I'm not going to into details of any letters to the editor that followed. Many of the comments as you see listed here were not specifically highly data driven, and I didn't think they deserved a lot of time given the short amount of time for the presentation. But in fairness, I just included the

list as well as a summary of Dr. Johnson's responses to those letters to the editor.

I also don't have time to go over the secondary aim publications, but I will point out that the first one, which is the most important, will be covered later by Dr. Summers when he addresses patients 65 years or older.

Thank you very much for your attention.

DR. TALAMINI: Thank you, Dr. Dachman.

Are there again brief clarification questions from Panel members? Dr. Steinberg?

DR. STEINBERG: So the colonoscopist was not blinded to the findings of the CTC?

DR. DACHMAN: No, they were blinded. There was no segmental unblinding. In other words, they were blinded at the time of the colonoscopy to the CTC results, but there was simply a comparison done post facto, no segmental unblinding.

DR. STEINBERG: So how did that work? They did the whole colonoscopy, and then they finished that, they took out polyps, and then someone took out and said, hey, the CTC showed a polyp in the sigmoid and you didn't see. They went back a second time?

DR. DACHMAN: That was not required by the trial for the optical colonoscopist to go back a second time. So we simply assume that

optical colonoscopy was truth. That's why we said the aim of the trial used colonoscopy as the reference standard, unlike the DOD trial.

DR. STEINBERG: But we know from Dr. Pickhardt's study that colonoscopy has its problems too. And so, how did you resolve a finding that was not found by the colonoscopist?

DR. DACHMAN: Right. Well, Dr. Pickhardt's trial was not published at the time this trial was planned. So I mean basically the idea was to address the concerns of the gastroenterology community, and therefore, keep it very straightforward. There were those who had complaints about segmental unblinding and how that might bias the gastroenterologists. There were actually concerns raised at some meetings about that, so we thought keep it clean and just make optical colonoscopy as the reference standard, with the exception that we did allow and encourage patients with CTC false positives at the 10 mm level to return within 90 days.

DR. TALAMINI: Dr. Imrey?

DR. IMREY: If I'm not mistaken, Dr. Pickhardt reported that approximately 50% of patients had positive lesions found, and you're reporting about 15% from your study. Is that solely a difference in how you deal with diminutive lesions, or is there some other difference between populations that needs to be considered?

DR. DACHMAN: No, I don't think there was a difference in populations. I mean it was a screening cohort. There were a certain number

of patients -- I think it might have been 10% or so that turned out in the end to be above average risk patients. But they all fit into American Cancer Society guidelines of the screening cohort.

DR. IMREY: Well, but that's a huge difference, 15% versus 50%.

DR. DACHMAN: And for what metric though? I mean so the ultimate metric here is neoplasia, so we separated out the neoplasia versus all polyps and all histologies, and that's real important. So in terms of the false -- the referral rate -- remember when -- the referral rate takes into account size only, not histology. So that's why we broke it down and reported the potential referral rate, if all histologies were taken into consideration.

DR. IMREY: All right. So the issue probably is then how you're dealing with these very small and histologically innocuous lesions?

DR. DACHMAN: Not necessarily small. But remember it's a post hoc evaluation of neoplasia only. That was common. That was a common denominator to both the DOD trial and the ACRIN trial. But the referral rate of the 12.8% is based only on size, 6 mm and larger.

DR. TALAMINI: Dr. Zhou?

DR. ZHOU: So I have clarifications. So if a patient has three polyps and then the CTC only able to detect two of them, is that a true positive or a true negative?

DR. DACHMAN: So the data as presented in both trials was by

patient and by polyp, so both of those data were given.

DR. ZHOU: No, I'm saying that --

DR. DACHMAN: So the 90% was the by-patient data.

DR. ZHOU: I know. But how do you calculate the per-patient sensitivity if you have three polyps, and then two has been correctly identified, but one has been wrongly identified? Is that positive or negative?

DR. DACHMAN: In the case of the by polyp --

DR. ZHOU: No, by patient.

DR. DACHMAN: I understand. In the case of the by patient, it's very simple. You can calculate sensitivity and specificity. In the case of the by polyp, specificity is a non sequitur. Each polyp and its size is considered an event, so you can calculate sensitivity.

DR. ZHOU: But your units of the data is at the polyp level, right? So you have to aggregate data from polyps to the patient level.

DR. DACHMAN: Right.

DR. ZHOU: So I mean if you have three polyps, but you're able to detect two of them, but one is missed, is that -- at the patient level is that true --

DR. DACHMAN: That's right. That's right. In the patient level, the logic of that and the reason that's the key metric is because -- and the logic of that is, is that in clinical practice, what makes a difference is whether you refer a patient to colonoscopy. The assumption is if a patient has

synchronous polyps, hopefully the gastroenterologist will detect those synchronous polyps. So we feel that the key metric, which really will ultimately deal with patient management, is the by-patient data. But in all fairness, of course, both data were presented.

DR. TALAMINI: Dr. Jiang?

DR. DACHMAN: So does that answer your question? So, if you find one polyp, it is a true positive by patient. If you find three polyps, each of those polyps are a separate event. The two polyps and their size are true positives. The one missed polyp is a false negative.

DR. ZHOU: So you have a two data point?

DR. DACHMAN: Two data sets.

DR. ZHOU: All right.

DR. DACHMAN: You have two separate calculations of the data, correct.

DR. TALAMINI: Dr. Jiang?

DR. JIANG: Clarification on the five false negatives for OC. Are those cancers adenomatous lesions, or what are they?

DR. DACHMAN: I believe they were -- none of them -- I don't think -- I don't know that any of -- none of them were cancers. They were adenomas. Most of them were adenomas, and one I think was inflammatory.

DR. TALAMINI: Dr. Fogel?

DR. FOGEL: Do you have any data regarding the number of

patients that were approached to participate in the study but did not enter the study because of exclusion criteria? So your 2600 represents 2600 out of what larger population?

DR. DACHMAN: No, that was -- the total accrual excluding duplicates was the 2600. Of those, there were eight patients that were ultimately deemed ineligible, and there were 10 patients who decided to withdraw. The only other ones that were not included in the cohort were things, for example, a couple of patients due to equipment failure, or inability to retrieve data from the trial. But I don't know any data on patients who were approached and refused.

DR. TALAMINI: Thank you for a great presentation.

Next is Dr. Bernard Levin, Professor Emeritus, University of Texas, MD Anderson Cancer Center.

Dr. Levin.

DR. LEVIN: Dr. Talamini and members of the Panel, my charge today is to review briefly for you and provide an overview of national guidelines promulgated by federal professional groups and by third party insurers. My disclosure, I have one non-significant one to report.

The outline of my presentation will be to briefly describe the objectives of screenings and then to provide an overview of guidelines provided by federal entities, professional societies, private third party insurers.

I just want to remind you of the objectives of screening for colorectal cancer. They include the systematic testing of asymptomatic individuals for pre-clinical disease, and prevent cancers by detecting and removing pre-malignant benign adenomas, as well as detecting surgically curable early colorectal cancer.

As you've already heard, the prevalence of adherence to screening is approximately 60% now in the U.S. compared to pap smears and mammography, which achieve a higher degree of adherence. Healthy Persons 2020 screening target for colorectal cancer screening is 70%.

The United States Public Service Task Force screening guidelines are summarized here. The use of fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults beginning at age 70 and continuing until age 75 are recommended. As you've heard, the evidence was deemed insufficient to assess the benefits and harms of CTC as a screening modality.

Some of the points of discussion by the USPSTF included two specific components. Potential preventable burden -- CTC could help reduce colorectal cancer mortality if patients who would otherwise refuse screening found it to be an acceptable alternative. The potential harms included the radiation from CTC, which were unknown, as well as the lifetime cumulative radiation risk from CTC and felt should be considered in the context of radiation exposure from other diagnostic and screening tests.

Other discussion points included reference to up to 16% of

people having their first CT colonography and the potential for extracolonic abnormalities that required further testing, as well as the inadequate evidence to assess the clinical consequences of identifying extracolonic abnormalities. But they concluded there was evidence for both benefit and harm.

In 2009 the Centers for Medicare and Medicaid Services concluded that the evidence is inadequate that CT colonography improves health outcomes in Medicare beneficiaries and suggested that well-designed clinical studies are needed in a Medicare population. And Medicare concluded that they would not cover -- it would not cover CT colonography for screening for colorectal cancer.

TRICARE, which is a military -- which covers uniformed health services, as well as individuals who are retirees and other beneficiaries, considered that CTC should be covered only when optical colonoscopy is medically contraindicated or cannot be completed. Medical contraindication could include people who are anticoagulated. The VA, United States Department of Veteran Affairs, does not recommend CTC for colorectal cancer screening.

So here is a summary of the federal entities once again. The USPSTF, current evidence is insufficient. The Centers for Medicare Services, it remains a non-covered benefit. The VA Health System does not recommend it for routine screening. And the military health system, or TRICARE, it's

covered only when optical colonoscopy is medically contraindicated or cannot be completed.

The American Cancer Society meeting with a multi-society task force, as well as the American College of Radiology, issued guidelines in 2008. The multi-society task force consisted of representatives from the American Gastroenterological Association, the American College of Gastroenterology, and the American Society for Gastrointestinal Endoscopy. Also participating were generalists and consumer health advocates and other advisors.

This group subdivided tests into two: tests that detected adenomatous polyps and cancer. And in this group were flexible sigmoidoscopy every five years, colonoscopy every 10 years, CTC every five years, and although it was recognized at the time that double contrast barium enema was on the decline, it was also included. As well as tests that primarily detect cancer: fecal occult blood test with high sensitivity for cancer, as well as FIT with high sensitivity for cancer, and stool DNA tests with high sensitivity for cancer at unknown intervals.

Major discussion points of this group included that CTC was comparable to optical colonoscopy for the detection of cancer of polyps of significant size when state of the art techniques are applied. Reasonable to repeat exams every five years, if the initial CTC is negative for polyps until further studies are completed. And there was acknowledgement that there was controversy over the long-term potential harms associated with radiation

dose effects because of the various models used. But there was potentially a long-term risk of cancer from repeated medical imaging exposures.

In 2011 based on the findings from the Kim and Pickhardt study, the American Gastroenterological Association concluded that the use of CT screening in Medicare-eligible patients 65 years and older was comparable to those observed in those of a low age general screening population.

In 2009 the American College of Gastroenterology updated its colorectal cancer screening guidelines and stated that the preferred screening test is optical colonoscopy every 10 years. Alternative prevention tests included CTC every five years as an alternative to colonoscopy every 10 years because of the recent performance in the ACRIN trial, which you just heard about. They based the conclusion that the principal performance feature that justifies inclusion of CTC as a viable alternative to colonoscopy is the 90% sensitivity for polyps 1 cm or larger size in the most recent multi-center U.S. trial.

The American College of Physicians issued a guidance statement in 2012, which was essentially a review of the existing literature, and recommended the use of a stool-based test, flexible sigmoidoscopy, or optical colonoscopy for those at average risk, and optical colonoscopy for those at higher risk. CTC was not specifically included in this recommendation. They also reviewed and concluded, based on the USPSTF,

that the evidence was insufficient to assess the benefits and harms of CTC.

The National Comprehensive Cancer Network, which is comprised of 22 major comprehensive cancer centers in the U.S., states that there's not a consensus on the use of CTC as a primary screening modality, and it is evolving with regards to recommendation and programmatic frequency, polyp size leading to referral for colonoscopy and a protocol for evaluating extracolonic lesions. If CTC is negative, that is, there are no polyps present, then repeat CTC in five years is appropriate, and if positive for polyps, colonoscopy should be performed.

The Institute for Clinical Systems Improvement in Minnesota has concluded in 2012 that CT colonography may be an option for CRC screening after incomplete screening or diagnostic colonoscopy and for anticoagulated patients who cannot safely discontinue anticoagulation therapy. This is based on their language, it's low quality evidence, and it's a weak recommendation.

So to summarize the professional groups, the ACS multi-society task force: American College of Radiology, CTC colonography every five years is an acceptable method of screening; American College of Gastroenterology, CTC every five years for those who decline colonoscopy; American College of Physicians, CTC not specifically recommended; the NCCN, not a consensus on CTC as a primary screening modality; and the Institute for Clinical Systems Improvement, use CTC after incomplete screening or for anticoagulated

individuals.

When one considers the array of third party insurers and private reimbursers, there are somewhat discrepant results. Kaiser Permanente does not recommend -- does not have CTC as a covered benefit. Neither does Aetna. United Healthcare it is approved; UniCare it's approved; Cigna, yes; and a variety of Blue Cross and Blue Shield insurers in many states have approved CTC as a covered benefit. It's worth a note that the Blue Cross Blue Shield technology evaluation group in 2009 stated that CT meets the criteria for an effective colorectal cancer screening test.

So, in summary, federal entities such as the USPSTF, CMS, the VA do not recommend CTC for screening of asymptomatic individuals 50 years and older. Considerable variation exists in the recommendations of professional organizations. And many but not all private or third party insurers cover CTC for colorectal cancer screening.

Thank you.

DR. TALAMINI: Thank you, Dr. Levin.

Clarification questions from Panel members? Yes?

DR. APPLEGATE: Yeah, I have a question or clarification. We just heard earlier from Dr Barlow that 15,000 members of the military have been screened with CT colonography from federal monies, and yet you stated that the military does not approve of this coverage. And so, I think that's -- I just want to understand, we have military people undergoing CT

colonography and yet you just stated that it's not recommended.

DR. LEVIN: I'm going to defer that question to someone in the military.

DR. APPLEGATE: So I mean there's multiple sites from my understating that are performing it and performing it -- from our earlier presenter that it's being performed well. So I just want to understand that.

DR. BARLOW: TRICARE is our healthcare -- our private insurance partner.

DR. APPLEGATE: I understand that. But I mean it sounded like that from your guideline review that it was not, you know, that it was not being recommended. And yet, our federal government has paid to have it performed by military hospitals.

DR. LEVIN: I can't explain the discrepancy, but if one looks at the TRICARE website, that is the language I've --

DR. APPLEGATE: I just want to, I just want to be clear on it.

DR. LURIE: Can I jump in for a second? I think the distinction is actually quite clear. There's the DOD and there's the VA, right?

DR. APPLEGATE: I'm not talking about the VA. I'm talking about military hospitals.

DR. LURIE: But the recommendation --

DR. APPLEGATE: Not VA.

DR. LURIE: The recommendation that Dr. Levin reviewed is for

the VA.

DR. LEVIN: No, I reviewed both.

DR. APPLEGATE: Right. He was talking about military hospitals, not the VA.

DR. LEVIN: I think --

DR. BARLOW: Can I clear that up?

DR. APPLEGATE: Yeah.

DR. TALAMINI: Dr. Dachman?

DR. APPLEGATE: They were separate --

DR. BARLOW: No, Dr. Barlow.

DR. TALAMINI: I'm sorry? I'm sorry. Dr. Barlow, yeah. Please speak in the microphone and identify yourself before answering please.

DR. BARLOW: Okay. Dr. Barlow, Senior Radiologist for the Colon Health Initiative at a military institution, Walter Reed.

The military has a -- TRICARE, which is a third party payer that helps provide services to military and retirees. Most of your active duties and military retirees through Space-A can get into the military hospitals, but a lot of them have to seek care out through their TRICARE partner, which is a standard HMO or healthcare insurance policy. So the policy for certain of the TRICARE companies that are providing the care may or may not cover VC, but we're doing it inside the MTFs.

So there's two treatment pathways that a military beneficiary

can get healthcare through. Either in the MTF, military treatment facility, or through TRICARE who's our partner. They were set up to handle healthcare that we couldn't provide the beneficiaries in the MTF. And they do provide a lot of healthcare benefits for military retirees.

DR. TALAMINI: Thank you. Further clarification questions for Dr. Levin? Dr. Glassman?

DR. GLASSMAN: Len Glassman. Question -- Dr. Levin, do you know of the federal groups that sort of followed the Preventive Services Task Force, was their look at the data a real independent from the ground up look, or did they simply read the Preventive Services Task Force report and put a stamp on it?

DR. LEVIN: CMS did its own independent review. It's a very thorough review of the information at that time. I'm unaware if the others did the same.

DR. TALAMINI: Dr. Steinberg?

DR. STEINBERG: I'm a little confused by the American College of Gastro recommendations. One of the pieces of information we were provided on the Panel was a letter sent by the ACG president and the ASGE president. And if I read that correctly, it said they do not recommend CTC as a screening tool. Your recommendations that you read off there said, yes, if the patient doesn't want a colonoscopy. Were you privy to the letter that the ASGE and the ACG sent in?

DR. LEVIN: Yes, I have seen the letter. It's public on their website. At the time of the ACS multi-site task force, there were -- representatives from those societies were a party to that. That was 2008. Subsequently, the letter that you have referred to, as well as the independent publication by the ACG in 2009, indicate a preference for colonoscopy as a primary screening test. That's as much as I've been privy to as those two documents.

DR. TALAMINI: So at this stage, if there are other clarification or more general questions for any of these three speakers, now would be the time regarding clinical trials. Are there other questions from Panel members?

DR. TALAMINI: Dr. Fogel.

DR. FOGEL: Is this the time to ask a more general question?

DR. TALAMINI: As long as it addresses these three speakers, yes.

DR. FOGEL: Yes. Screening colonoscopy is not a one-shot event, but rather something that takes place over 25 or possibly 30 years. Do you have any thoughts based on the published literature regarding the way to follow up patients after their initial screening study, assuming that it is negative?

DR. LEVIN: Well, I can start taking a crack at that one. There's certainly a lot of discussion currently about whether there is any benefit for interim testing within the 10-year period. There's no definitive of which I'm

aware that addresses that specifically. But, of course, the combination of an invasive test plus subsequent non-invasive tests would be certainly feasible and might have provided a degree of assurance that the 10-year interval, which seems reasonable at the moment, could be strengthened.

DR. TALAMINI: Dr. Kelsen?

DR. KELSEN: As sort of a follow-up to that, but also to an earlier question, I know we're focusing on CTC, but I was struck that a simple stool test, say FIT, if it's done regularly seemed competitive with either of these two invasive or semi-invasive approaches, optical colonoscopy or CTC. And the answer I got back was that there are no current data available to say that that's true or not. So are there plans to do a study which would use modern stool based technology performed in a physician's office or some way so people would actually do it? Or is this a question that is still not going to be addressed in the near future, to your knowledge?

DR. LEVIN: Well, there seems little doubt that FIT is superior to the old guiaic fecal occult blood, and possibly even superior to the highest sensitivity non-fecal immunochemical test. And there are at least two randomized controlled trials comparing FIT to optical colonoscopy -- one in the U.S. and one in Europe -- that will eventually answer those questions definitively, but not for some years.

DR. TALAMINI: Dr. Charabaty?

DR. CHARABATY: Yes, I have a question for Dr. Pickhardt

or Dr. Dachman. When I initially read Dr. Pickhardt's study that was published in the *New England Journal of Medicine,* I think it was very exciting and there was a big buzz. But it seemed to me from the ACRIN study and other studies I've seen -- and I'm not an expert in CTC -- that the degree of sensitivity and specificity that was reached in the first study by Dr. Pickhardt was never replicated as well, that 90% or more. We heard from Dr. Dachman that the specificity for polyps more than 10 mm was 86%. And I was surprised to see that in your first study there were some limitations. You used room air. The patient was insufflating the tube. And then, now we know that things are much better.

So how do you explain that? You know, even though the ACRIN study looked at community doctors, but they were also like the best radiologists doing that also. They were not community radiologists as we understand.

DR. PICKHARDT: Well, sure, and I'll have Dr. Dachman address this as well. But there are other studies, which I think we'll hear about in the public comments, that achieved similar results to ours, actually slightly superior when using this primary 3D approach. In Europe there have been papers -- trials that have achieved high 90s, so there -- and I would argue that the ACRIN results were comparable. I think we could argue about certain differences in software, stool tagging techniques, and it gets fairly complex if you start to really get to the bottom of it. But I think the results from all

these trials have been I think encouraging and certainly above the threshold that we were shooting for.

DR. CHARABATY: Thank you.

DR. PICKHARDT: I would like to also quickly clarify. I think, Dr. Imrey, you had a question about the different prevalence between DOD and the ACRIN. Actually they were almost identical. I think it was 4% had adenomas 1 cm or larger and about 14% at the 6 mm for both studies. They're almost identical. The 50% includes that thousand diminutive lesions, which if -- I don't know if we got into the details of diminutives, but that's where it gets up to 40 or 50% if you include those, so I just wanted to make that clear.

DR. TALAMINI: Thank you very much.

DR. CHARABATY: I have one more question. We heard from a lot of people that there was a question of compliance. People brought up FIT, and then the downside is that maybe the compliance was not there. So with compliance, keeping in mind this, when on virtual colonoscopy, you might not be able to detect polyps that are 6 or less than 10 mm, or between 6 and 9 or less -- or Dr. Barlow mentioned that sub-6 polyps were not even mentioned in the report.

And I'm wondering, you know, then you're relying on the fact that the CTC is going to be done five years later, so if any of these polyps grew or become insignificant, you cannot pick that up. As opposed with

optical colonoscopy, even the small polyps we're going to pick them up, so that decreases the worry and that's why, you know, maybe the interval is different.

So I was wondering if in your studies, now that you have probably more than five years doing that, how compliant have you seen patients coming back for their next CTC at five years? And can you confidently say that whatever was not reported or missed -- the small ones that are not significant at that time are not missed the second time because the patient didn't show up for their next screening test?

DR. PICKHARDT: Right. That's a great question. We actually do have an update on that now. And I would say it's not simply because we can't detect diminutive lesions. We can and probably are about 50% sensitive for all of those. We choose not to -- and it's a conscious decision -- because of the increased obviously utilization, increased complications and costs simply don't -- it just -- they don't justify their referral to colonoscopy.

Now, we've looked at our cancer rates in patients five years out from a screening colonoscopy -- a screening CTC that was negative. That is, we ignored diminutives. All we know is that we didn't call anything non-diminutive. And the interval cancer rate was less than typical colonoscopy. There was one cancer in that entire experience, which is less than the interval cancer rate at colonoscopy. So I think we've shown that we can safely ignore diminutive lesions. That paper may have -- may be addressed in later

sessions, but that's a very important point.

Did you have any comments on that?

DR. TALAMINI: Quickly.

DR. DACHMAN: Yes, I'd like to address Dr. Charabaty's previous question about the specificity. So just recognizing that in the ACRIN trial and at the time that it was done, the focus was on maximizing sensitivity, and there were 15 radiologists. Remember -- I don't know if it was broken down specifically in the paper, but my recollection in the planning of this was that at least five of the radiologists were completely new to virtual colonoscopy and underwent training that we would now consider -- white paper guidelines -- adequate training.

So that would be the equivalent -- let's say the gastroenterologist just finishing fellowship, getting out -- you took a test, yes. You passed, but you're certainly not the same as the experienced radiologist. So it was the combination of being tested based on sensitivity that I think -- and the inexperienced radiologists. And if you look at -- in the paper I actually had a follow-up slide there. It's, I think, in your handout. Seven radiologists had 100% sensitivity, and I think they also had high specificity.

And there were two radiologists -- three radiologists who had very low sensitivity and I believe also had low specificity. And they -- we don't know which ones were which, but they were the highest recruiters. So the n of patients was weighted towards that low specificity, and I think it's

explained by that factor.

DR. TALAMINI: Dr. Zhou?

DR. ZHOU: So I have actually three questions. So the first one is how can you show the patient -- for both studies -- probably internal medicine. How you do show the patient population you have actually is representative of the population in general as average risk?

DR. PICKHARDT: Well, simply, I think we showed our inclusion/exclusion criteria. Obviously there may be regional differences depending on where the studies were performed, but I know of no other way to say that they simply represent the typical screening population in that area.

DR. ZHOU: But you could look at the characteristics of the general population versus the sample population you have, if they're similar or not.

DR. PICKHARDT: And that's true. These are -- relatively speaking these are not very large studies, so I don't -- and I don't know -- did you get into ethnic or racial breakdown of the ACRIN trial?

DR. DACHMAN: Well, I mean I showed the gender and age, which I think were fairly reasonable and representative. But basically, it's followed the American Cancer Society guidelines in terms of what defined patients as screening patients. And that's why I listed in those slides the exclusion criteria that you have in your slides. Now, I also mentioned --

although not the slides -- that in retrospect when you look at increased risk -- in other words, did you have a family member with a history of colon cancer? That might have increased your risk. There were I believe about 9% of patients that would have fallen into increased risk, but still be -- meet the criteria for screening patients. I think you could just look at historical, published historicals to see if that fits an average screening population.

DR. ZHOU: Well, because this would depend on how you recruit the patients. Are those patients actually come to the clinic for something else for some problem? The reason they come to the study is because they have to go to hospital to -- for some problem they have or are you recruited for general public -- general population?

DR. PICKHARDT: By definition they're asymptomatic and undergoing -- they're coming for colorectal cancer screening as asymptomatic adults. I don't -- there are no symptomatic patients in this -- in either trial.

DR. DACHMAN: Right. So I mean the way to recruit for a trial like this is you'll deal directly with the primary care physician. When that physician has somebody who's due for colorectal cancer screening, they simply recruit them with sort of a line like, hey, you know, we have this trial going on. You can have a one-day prep. You don't need to lose another day of work. Just agree to have a virtual colonoscopy on the same day, so it doesn't really --

DR. PICKHARDT: And I think the low prevalence of adenomas

obviously reflects that this is a very healthy screening population. I mean if you look at symptomatic cohorts, the rates are much higher.

DR. TALAMINI: Next question, Dr. Zhou.

DR. ZHOU: So much more concern I have with is about the gold standards you have that both study used. The first study, I think, one of the problem with gold standard is the reference standard actually is depend on the test results you want to evaluate, which as we know that's a real clear bias. So second study they are -- from the CTC, but still the OC still has -- is imperfect. I wonder you have that both study evaluate what the consequences of use those imperfect gold standard on estimating sensitivity and specificity. I think they could go down the estimate sensitivities if you take into consideration of the imperfect gold standard you use.

DR. PICKHARDT: That's possible. But then, of course, the performance of the colonoscopy would also fall at the same rate, if we're assuming both tests are missing significant lesions. In reality, there is no perfect gold standard. I think as close as we can get as an endoscopist who's aware of the findings in our trial that represented our enhanced reference standard. I realize that's not perfect, and there are still lesions missed. Some of those CTC false positives are -- turn out to be false negatives. And we have no way of reconciling that at the time of the trial.

DR. ZHOU: Well, but I would say that you do have estimated sensitivity and specificity with OC from other studies. So you use that

number you could -- so that you don't give that number -- the sensitivity and specificity to OC?

DR. PICKHARDT: No, because that's even harder because all the old trials basing -- for colonoscopy sensitivity or performance is based on back-to-back optical colonoscopies where one endoscopist does a colonoscopy, walks out of the room, a second one comes in, does a colonoscopy, maybe a different day, but usually back to back. And obviously that's even worse of a reference standard because there can be systematic misses because you're not doing anything different. You're just applying the same test twice. Does that make sense?

DR. ZHOU: Well, but do you -- in those paper, you do give estimates in sensitivity and specificity for OC. So you're saying those numbers are not trustworthy?

DR. PICKHARDT: No. But that's a different trial. For our trial, we were unblinding results of a different test, virtual colonoscopy, and they were actually trying to find their own misses to estimate sensitivity. This is the first time a new test had been applied to evaluate colonoscopy. Previously we never had a second test to try to determine are they missing lesions? I think it was just assumed it was perfect at that point.

DR. DACHMAN: I mean the ACRIN paper did not do that. So it only did that for those small subset of patients who went back within 90 days, the 15 patients who ultimately complied to have a colonoscopy. But the

segmental unblinding study did allow comparison to optical colonoscopy since as Dr. Pickhardt explained the new gold standard is the second look after segmental unblinding.

DR. TALAMINI: So this will have to be our last question.

Dr. Steinberg?

DR. STEINBERG: I actually have two, if you'll permit me. Can we say now since we have so many years behind us of screening CTCs what the perforation is overall in the community and these centers of excellence? What do you quote?

DR. PICKHARDT: It is difficult to get it. It is very -- it's very low at screening with the use of CO_2. Another thing you have to realize is a perforation at CTC doesn't equal a perforation at colonoscopy. That is, we see gas outside of the lumen in asymptomatic patients, for example. We haven't had in our center, but I believe one of the cases Dr. Barlow was talking about, it was an asymptomatic perforation. At colonoscopy that's not detectable.

DR. STEINBERG: Clinically significant perforations.

DR. PICKHARDT: Okay. That's --

DR. STEINBERG: Can you give us a number?

DR. PICKHARDT: I believe .005. Is that the number?

DR. STEINBERG: Percent?

DR. PICKHARDT: Yes, percent based on, based on about -- at

the time we had 20,000 -- and we had an international cohort, and it was I believe one symptomatic perforation -- am I getting that right? One out of 25,000 or something it was.

DR. DACHMAN: Well, we have two from the military out of 15,000.

DR. PICKHARDT: Right. And one of those was asymptomatic. So realize -- at colonoscopy you cannot diagnose an asymptomatic perforation because there --

DR. STEINBERG: Right.

DR. PICKHARDT: And there is air outside of the colon about 1% of colonoscopies.

DR. STEINBERG: Right.

DR. PICKHARDT: Those would be called perforations at CTC. So they're very different rates we're talking about, so we have to talk about symptomatic. So they have 1 in 15,000 plus 1 in 20,000, so you could consider -- the numbers are very small, obviously.

DR STEINBERG: They are small.

DR. PICKHARDT: Two out of, you know, 40,000. I don't know what that --

DR. STEINBERG: My second question is about the Medicare population. I believe that the reason that -- one of the main reasons that CMS declined to cover screening CTCs was that there was an insufficient

amount of data on the population over the age of 65. That was in 2008, I believe. And that is a significant barrier for Medicare patients not having CTCs, screening CTCs.

So the question is, since 2008 do we have sufficient data on the population over 65, and is CMS -- I don't know if you're privy to this -- going to revisit this issue in terms of covering that population? But maybe you could tell us the over-65 data.

DR. DACHMAN: Well, that data will be presented. So in my last slide of the secondary aim papers, I mentioned, number one was Johnson et al., covering exactly that for the ACRIN trial. And that will be covered in Dr. Summers' presentation in more detail.

DR. LEVIN: I'm not aware of any current recommendations from CMS other than I believe they are going to be taking it under review.

DR. TALAMINI: Okay. I'd like to thank our speakers and the Panel for excellent questions. And we'll move on to the radiation risk section, and we're about 15 minutes behind at this stage.

The next speaker is Dr. Amy Berrington de Gonzalez, Senior Investigator, Division of Cancer Epidemiology and Genetics with the National Cancer Institute.

DR. BERRINGTON DE GONZALEZ: Thank you for inviting me to come and speak today.

I'm a radiation epidemiologist, and I specialize in estimating

cancer risks from medical radiation exposures and wherever possible comparing them to the benefits. I'm a federal employee, so I have no disclosures.

So a recent report by the National Council on Radiation Protection estimated that average annual radiation exposure to the U.S. population had almost doubled in the last 30 years. And that's primarily because of the increase in the use of medical radiation exposure. You can see here the large increase in the size of the yellow portion of the pie.

So in 1980 it was estimated that on average there was about 0.5 mSv per person per year for medical exposures, and that in 2006 this had increased to about 3 mSv, so a six-fold increase in medical radiation. And this is primarily driven by the use of CT scans, as you can see, from 3 million to 70 million. But actually all other diagnostic radiation exposures have increased as well: conventional x-ray and also an important contribution is nuclear medicine.

So as I said, the key contribution, the key concern is the increase in CT scan use. And this figure here shows the pattern over the last 15 years -- the estimated number of CTs performed every year, so between 5 to 10% increase annually. And the rate of change increased in the late 1990s, which was when the multi-detector CT was introduced, so it was quicker to conduct CT scans and the performance was better.

So the NCRP report was published around -- the results were

first made available around 2006-2007, and this figure extends results up to 2010. And you see there's no change in the trend. The increase is basically continued. 2010 is the last date of estimated 82 million CT scans performed.

So it's not just the number of CT scans that makes us concerned about the radiation exposure from the source. It's also that the average dose per CT scan is typically about 10 times higher than the dose you would get if you performed a conventional x-ray to the same region of the body. So these tables here show what we call effective doses and then also organ doses. So I'll just take a couple of minutes to explain this system because I'm going to use it throughout the presentation.

So in the top table here we have the estimated effective dose for either a conventional x-ray or CT scan. So you see conventional abdomen CT is about 8 mSv. In the bottom box we show the estimated organ doses to different parts of the body from this same type of CT scan. So the CT scan or an x-ray obviously highly non-uniform across the body. So an abdomen CT gives 20 mGy on average to the stomach and no exposure to the brain. If we just look at the organ doses, it can be difficult to compare different types of exposure and say what's high dose and what's low dose.

And so that's where the system of effective dose was developed, which is effectively an average -- so you average the organ doses across the body taking into account the radio sensitivity of each of the organs. And so, you'll see that -- I'll use effective dose on several occasions to

compare different types of procedures, but when we do any risk calculation, it's using organ dose, the amount of radiation actually estimated to each organ in the body. 1 mGy is effectively the same from a risk perspective as 1 mSv. They're just representing slightly different things.

So when we come to using CT for screening, there are even more concerns because, as I said, the doses tend to be higher than conventional x-ray. And, of course, with screening you're now talking about exposing large numbers of asymptomatic individuals who will not benefit from radiation, and these were people who cannot benefit from the screening test.

When we look at the radiation risks from these exposures, an important aspect of the risk to consider is that after exposure to radiation, all studies pretty much have shown that the risk of radiation-related cancer remains elevated for the remainder of your lifetime. So when we talk about radiation risk we're usually talking about lifetime risk. And so, the younger you are when you're exposed, the longer you have to accumulate risk. And also, studies have shown that people who are younger tend to be more radiosensitive.

So you put those two aspects together, higher radiosensitivity and longer life expectancy, the younger you are when you're exposed, the higher typically the radiation risk from the same dose. On the other hand, if you screen people at younger ages, particularly for something like cancer,

typically it's less common at younger ages. So the absolute benefit from screening will be lower and the radiation risk will be higher.

So whenever we look at CT screening or screening mammography, for example, we always want to look carefully at the risk/benefit ratio according to age, not just across the whole screening interval. And, of course, there's also the additional concerns about additional radiation exposure from follow-up examinations.

So here's a comparison of typical doses then shown in terms of the effective dose for different types of screening examinations. So the low dose lung CT screen, the type that was used in the recent national lung screening trial, is about 1 mSv, mammography is about 0.5 mSv. That's because basically it only exposes the breast. No other organs are exposed. I get asked a lot now about airport scanners, so for comparison you have to have about -- you have to go through the airport scanner about 10,000 times for that to give you the same dose as one lung CT screen.

Calcium scoring or coronary artery calcification screening about 3 mSv, and for the study that I'm going to show today, we used the ACRIN protocols for estimating dose. And so, we estimated about 7 mSv. But as you saw from the current work that they're doing in the military, certainly the dose can be somewhat lower than that. Whole body CT, which almost no one recommends, is the highest of the screening tools, about 12 mSv.

So CT colonography is even with some of these lower doses --

so I think Dr. Barlow said that they do it -- they have doses as low as 3 mSv -- it still puts it sort of at the top of the range of current radiation-related screening tools. So there were obviously concerns about what the potential radiation risks might be from using this tool to screen people routinely.

So with some colleagues from the CISNET group, the NCI CISNET group, which is a group of individuals -- a group of lots of different universities who developed screening models -- I conducted a study to look at -- to estimate what the risks might be from routine CT colonography screening, both according to the age at a single screen and also looking at the cumulative effect from long-term screening. We considered the impact of extra CT scans conducted for extracolonic findings, and it was the CISNET group's estimates of the number of cancers that were prevented by screening that we used to do the risk/benefit ratio comparison.

Now, all of these things are very difficult to study directly, particularly the radiation risks. As I've said, the radiation-related cancers would typically occur over the rest of someone's lifetime. And so, to actually do a study directly to estimate these risks, you would have to follow the patients up for many decades, and you would need very large studies. So in order to get an answer without have to wait for another 30 years, we typically used modeling studies, and I'll explain how we did that. And in this case, we used modeling for both the risks and the benefits, as was being discussed already today. There haven't been any direct trials that have

actually looked at and estimated the efficacy directly of CT colonography.

So, some background about the radiation risk modeling then. And the basis for the modeling we do is what's really known about low dose ionizing radiation and cancer risk. And the gold standard study is the long-term study of the Japanese atomic bomb survivors.

So the common misconception about this study is that it's a high dose study. Actually, the survivors in the study -- there's about 100,000 of them -- were exposed to a wide range of doses up to about 2 Gy -- people who were exposed up to about 2 Gy were included in the study. About 60% of the survivors in the study actually had doses of less than 100 mGy. And you remember when I was showing the organ doses for conventional CT of the abdomen, then they give doses of about 20 mGy to the stomach or the colon.

So there's a lot of information in this study about risks from low doses of radiation as well as the risks from much higher doses. The study has shown that the risk is basically linear with doses right down to low doses. As I say, the risk remains elevated throughout life. They've got 60 years follow-up now on these people. And they've shown that radiation can cause most cancers and that the risks are higher for younger ages of exposure.

So we'll then -- do you have a question?

UNIDENTIFIED SPEAKER: Could you just interpret the curves on that graph?

DR. BERRINGTON DE GONZALEZ: Sure. So the gray points are the actual data points, if you look at categories of dose, so if you divide people up into bins of dose level. And then the black line is the fitted linear dose response. And if you allow the fit -- rather than forcing it to be linear, but fitting -- allowing it to fit through all the points, you can see it's slightly -- it's very slightly non-linear. But basically there's no evidence of significant departure from linearity.

Although the Japanese atomic bomb survivors are the basis for most radiation protection standards, there's many other long-term radiation epidemiology studies that are used as supportive evidence. And those include three key studies that actually looked at cancer risks in medical radiation exposures directly and looked at effectively either diagnostic tests or procedures with quite low doses. These were all conducted by the National Cancer Institute, and they include a cohort of children who had scalp radiation to treat tinea capitis. They had a threefold risk of thyroid cancer for doses in the range of 40 to 80 mGy. That's about a couple of CT scans.

There's also a cohort of young women with scoliosis who had repeated spine x-rays. In those women, those who had more than 100 mGy had a twofold increased risk of breast cancer. And a long-term study of patients with tuberculosis who had repeated fluoroscopy to monitor their TB, they had -- so each fluoroscopy is really a pretty small dose, but these patients had -- some of them had hundreds of these exams. And so, it

accumulated up to large doses. They had a twofold increased risk of breast cancer, even those in the lower dose range.

So these studies all show just in principle that there is direct evidence as well that if you give small doses of radiation for medical exposures, we have seen that in these populations, we can detect increased cancer risks. Yes?

DR. APPLEGATE: Just as a clarification, can you note that the top two studies were in children, and they were at higher risk for later cancer?

DR. BERRINGTON DE GONZALEZ: Yes, the --

DR. APPLEGATE: Thanks.

DR. BERRINGTON DE GONZALEZ: Yes, the thyroid cancer increased risk with childhood exposure. The scoliosis includes -- it's young women, but also they had exposures through into adulthood.

So, until recently though there was no direct evidence -- there were no studies that looked directly at CT scans themselves. So whenever we'd present results based on these risk models, people would always say, oh well, but -- yes, it's very interesting, but no one's actually seen directly the cancer risks after CT scans.

We just finished though last year the first follow-up of the UK NCI pediatric CT scan study, which was a retrospective cohort study. So because of this need typically to wait a long time to see radiation-related

cancer risks, we did the study the other way around. We linked registries back in time, effectively. It's equally valid to a prospective cohort study. It just means you don't have to wait as long.

So we took radiology information system databases from over 100 hospitals in the UK and linked them to the National Cancer Registry. So we took patients who had their first CT scan up to the age of 21. By linking them to the cancer registry, we ensured that they were -- we only included patients who didn't have cancer at the time of their first CT scan. And then we also made this further exclusion that we only looked at any cancers that occurred either two years for leukemia or five years for brain tumors after the first CT scan to try to remove the possibility that they were having the CT scan as part of the diagnostic workup process. So really trying to only evaluate CT scans that could have possibly caused a cancer.

We got an average of follow-up of about 10 years currently in this cohort -- the oldest patient who's 42. And as of the follow-up last year, we had 74 leukemias and 135 brain tumors. So these were the cancers that we planned to analyze first, the high radiosensitive and then the common childhood cancers. Of all of those, about 300 CT scans in the analysis and typical breakdown that you would expect in children shown here.

So these are the results that we published last year in the *Lancet*. So this is the dose response relationship for leukemia in relation to the estimated radiation dose to the red bone marrow. So we saw clear

evidence of basically linear increased risk with increased cumulative red bone marrow dose and a significant linear trend. Same findings for brain tumors and radiation dose, so the -- and highly significant linear trend. So really this study showed for the first time some evidence that it is possible that CT scans can result in subsequent cancer risks in children.

One of the important steps then is -- and this is done routinely in all radiation epidemiology -- is to compare your results back to the lifespan study of the Japanese atomic bomb survivors because that's what's used typically to project the risks. And you'll see in a minute that's what I used. So we want to know, is the slope of the dose response from our CT study per unit dose what we would have expected -- or what we saw also in the lifespan study of the Japanese?

So if we make the same restriction, follow-up period, and age at exposure to really make the Japanese cohort like our study, then you can see that for leukemia, this is the risk per mGy. It was very similar in our CT scan study and the lifespan study. For brain tumors, the risk in our study was about four times higher than in the lifespan study, but still technically compatible. You see that there's actually a very wide confidence interval for the lifespan study for brain tumors at that age.

So this is some additional reassurance that using risk models in the Japanese atomic bomb survivors is a valid approach for estimating radiation risks from medical radiation exposures.

There's already been external validation of our results earlier this year in the *BMJ*. The Australians published their results. They have a very similarly constructed cohort. They have 600,000 children, and they also included an unexposed population. Their study is based on Australian Medicare. They did the analysis in a lot of different ways, so it's difficult to compare directly. But basically they saw a linear dose response with number of CT scans. And when they turned that into the estimated excess cancers, they estimate about one excess cancer per 2,000. And, again, that's compatible with the Japanese atomic bomb survivors.

So when we do the radiation risk modeling for the CT colonography then -- the background I've just given you is to show why we think that it's a reasonable approach to use the Japanese atomic bomb survivors as the basis for lifetime risk projections. And so, for the CT colonography study, we built some risk models in an online computer program called NCI RadRAT. And these risk models are based on the National Academy of Science BEIR VII report. This is a published report by a group of experts. And we used their approach, and then expanded it slightly to include some extra cancer sites that they didn't include in their initial evaluation.

This is the input screen from our freely online version. And what you're basically required to do -- this is a tool for -- not for the general public. It's for researchers because you need estimates of the organ dose from the exposure that you're interested in. But you input the age of the

exposure or the birth year, exposure year, the organs that are exposed, and then it produced an estimate of the lifetime radiation-related cancer risk.

A key aspect of this tool is that it takes into account a number of uncertainties. So you don't just get a central estimate. You get a uncertainty limit with this central estimate. And that takes into account a number of uncertainties, including what we call subjective uncertainties of how you transfer risks in the Japanese population to the U.S. population that has quite different background cancer rates. It takes into account the impact of the dose level and the dose rate. So that's whether the dose was delivered all in one go or delivered in small fractions over time. And it also takes into account statistical uncertainties in the model parameters.

So, just one comment then on the basic approach. So we're using what's called the linear no-threshold model as the underlying assumption for the radiation risks that I'm going to present. And there's ongoing discussion, controversy if you want to call it that, about this model. And so, I wanted to present here just some of the alternatives so that you're aware of -- if you want to take a different position, what they might do to the radiation risks.

So what I'm going to show today is based primarily on assuming this red line here, that no matter how low the dose, the risk is approximately linear in dose. And that fits well with the epidemiological evidence. There's biological and experimental evidence that suggests possibly alternative

models. And those include things like a threshold model, where there's a dose below which there's no risk of cancer, or one even where -- what's called a hormetic model where low doses of radiation may actually be good for you. There's also a downward curving possibility based on some experimental evidence. And that would mean that at low doses, actually the risks would be slightly higher than the ones that we estimate.

There's lots of reports describing the different positions. I've shown one here. This was a comparison debate that we published in *Radiology* a few years ago summarizing the evidence for and against the linear no-threshold. So it's an accepted model though for radiation protection purposes and, as I say, the alternatives could result in both higher risks or lower risks. So this is sort of middle ground.

Just going back to the doses, so we've got this risk model. We then need to input estimates of the radiation doses. And these were estimated using the ACRIN trial protocols. We had applied the trial protocols to nine different types of CT scanners, and we have some software called NCI CT dose software that was developed by one of our health physicists and uses state of the art phantoms, which are shown here. You apply the radiation to the different organs according to age at exposure, and you can get very good estimates of what the typical doses will be to all the different parts of the body. And this is also software that's available for other researchers to use.

These are our estimates of what a typical CT colonography

screen -- the doses it will give to the different organs, assuming -- well, with a summary effective dose of about 7 to 8 mSv. So if you think that the doses can be reduced like Dr. Barlow suggests to more like an effective dose of 3 or 4 mSv, then all these organ doses will be halved. But we were using the ACRIN protocols, and so these are the typical organ dose estimates. So most of the organs really in the -- that receive the full scan get around 10 mGy, and then the 6 mGy to the red bone marrow.

So we input those organ dose estimates into our risk estimation program and then sum the risk across all the different types of cancer to get to a total cumulative risk of radiation-related cancer incidence. So these are our estimates for women for one single CT colonography screen according to age, and we went right back to age 30 just to show -- really demonstrate that there is some age dependence of risk.

So for the sorts of screening agents we're really talking about, though, one screen gives an estimated 30 to 60 radiation-related cancers per 100,00 screens. The uncertainty limits that are shown here take into account some of those uncertainties you can approximately -- which suggests the risk could be approximately half that or up to not quite double that.

So to compare these risks though to the potential benefits, we wanted to look at a full screening program. So that's where we collaborated as I said with the NCI CISNET micro-simulation group. And there are groups -- there are CISNET groups that look at many different cancer sites, and they

develop models to try and simulate the natural history of a particular cancer and then to look at what happens if you put in some intervention like screening.

So these models -- for colorectal cancer, there were three models that were developed by independent groups. And they're from Massachusetts General Hospital, from the Netherlands, from University of Minnesota, a whole range of people collaborate on these. And they developed the models independently and then -- but using a sort of systematic approach, and then put them together to compare them. So we used all three models for the comparison of the potential benefits.

All these models used the test characteristics based on the ACRIN trial, which you heard about earlier, and then used standard colonoscopy follow-up protocols both for -- immediately after the screen, but also for the typical process that patients went into after a positive screen and for the remainder of their screening program. And the details of these models are in this *JNCI* paper by Amy Knudsen.

Now, this is the underlying idea of these models. So you take a patient, you start with a cohort of 100,000 people, and you take them through this natural history where they start with no lesion. And then every year they have a probability of transitioning into one of these next states. And then you input screening -- it can either impact here or here, either removal of the adenoma or early detection of the cancer. And in this case,

the screening that they were inputting was the CT colonography screening.

They calibrate without the screening, and they calibrate the data from autopsy studies and see the cancer incidence data that was pre-screening in order to try and make sure that their model is basically predicting cancer incidence rates correctly.

So here's the main results from our study, so this is really the key slide. This is the comparison of the number of cancers that could be prevented by CT colonography screening every five years compared to the number of radiation-induced cancers. The results were basically similar for men and women, so they're shown combined here. So the blue bars are the number of cancers prevented and the red bars the estimated number of radiation-induced cancers.

This is the age at screening. So we look, first of all, at the full screening program, a typical recommendation age 50 to 80 years. You can see even if the estimated benefits of being quite significantly overestimated or the radiation induced risks have been severely underestimated, that wouldn't change our conclusion that the radiation risks are much, much smaller than the number of cancers prevented by screening. If you go out back to starting at age 40, this is just showing for comparison the radiation risks go up a bit. The benefits don't go up very much because of course colorectal cancer is rare before age 50.

We then wanted to break this full screening program down to

really show how the benefits and risks compare by age. This, as I said, is a standard question we always want to look at because the risk/benefit ratio tends to be greater for older ages. And that's shown very clearly here, that if you look at the older age patients, then in terms of the radiation risks, they're even smaller and you've got a lot of benefits still. Even for the 50- to 64-year-olds, it looks very good. But when you get down to the 40- to 49-year-olds, that's where you're getting into territory where you certainly -- I wouldn't say for certain that the radiation risks are much smaller than the benefits.

These are the ratio of the numbers of cancers prevented for the number of cancers induced. So that gives you some idea of how wrong you would have to be on either side of the equation to actually change your conclusion. You would have to have overestimated the benefits by 20-fold or underestimated the radiation risks 20-fold to change your conclusion about screening in this 50 to 80 age range.

So that main calculation doesn't include the radiation risks from the extracolonic findings, from the follow-up CT scans for extracolonic findings. There haven't been any studies, at least when we published our paper, that looked long term at how many follow-up CT scans people tended to have. But there were three studies that had looked at how many follow-up studies people had just after the first screen.

So we looked at these three studies and counted how many follow-up scans the patient had. Either abdomen/pelvis, chest, CT, or whole

body were the most common. We can then go through the same process where we estimate the number of radiation-related cancers that you might get from those follow-up CT scans and sum them over all the types of CT scans.

So there's very wide variation in the estimates of the number of follow-up scans, but basically, whichever study you pick, even the one with the highest number of follow-up CT scans, the number of additional cancers is still very small than the estimated number from the single CT colonography screen itself. And that's because for the CT colonography screen, everyone's getting that exposure. This is about 10% of the population getting a follow-up CT scan, so you're still adding on average -- in your 100,000 people, you're still adding not very much radiation exposure.

Probably as you go out in time with more follow-up repeat colonoscopy -- colonography screens, this rate of extracolonic findings would go down over time. And so, I think that for the subsequent screens, the number of excess scans, and therefore, the number of radiation-induced cancers would decrease further. So our conclusion from this was although in our main calculations we didn't include these extracolonic -- these CT scans for extracolonic findings, it wouldn't change the overall risk/benefit ratio in a material way.

So really the main reason that this risk/benefit ration for CT colonography really looks very good is the benefit from -- the potential

benefit from the screening. I've just shown here for comparison some estimated benefits from a full mammography screening program, and also lung CT screening. And you can see that CT colonography really does very well. You're removing the cancer and not just preventing the death from the cancer. So this is a comparison in terms of deaths prevented.

Mammography annual screening, we estimate it prevents about 500 deaths per 100,000 screened. If you use lung CT in heavy smokers, the number could also be very large. And that's, of course, because this is a very high-risk population that you're talking about, so you've got an estimated 20% reduction in mortality, but in a very high-risk population. CT colonography, as I say the key difference is that you're removing these cancers, not just preventing the deaths.

For comparison, I was also trying to estimate a similar figure for cervical cancer screening. And that's not -- it's quite difficult to do because it's so effective and the rates -- the cervical cancer rates have been so affected by it. But I think it's probably around about 100 per 100,000 screened, probably from age 30 to 60 or 30 to 50.

So, the conclusions from our study then. That based on the assumptions that I explained, our results suggest that the radiation-related cancer risks are much smaller than the estimated benefits for CT colonography screening every five years from about age 50 to 80. If we included additional radiation risks from extracolonic findings, I don't think

that would alter this conclusion. Of course, our results are based on models, not direct studies. But, nevertheless, since we published our modeled estimates, we also did then publish the first study, which suggested some evidence of direct -- direct evidence of cancer risks after pediatric CT scans.

We included the known unknowns in our model assumptions in order to look at the uncertainties. There's always the unknown unknowns. And, of course, I think that there are a number of studies now that show that the doses could be reduced further than the dose level that we assumed in our calculations. Basically, the radiation risks are proportional to dose. If you can half the radiation dose, you'll half the radiation risks that I presented.

I'd just like to finish with acknowledging all the collaborators in this study. Thank you.

DR. TALAMINI: Thank you. A very clear presentation.

Dr. Dauer, I think you have a question?

DR. DAUER: Yes. When you first talked about the UK study involving the pediatric patients, I didn't see in there where you did a comparison with patients that were not given CT scans. You did that -- that was done in the Australian study, but that wasn't done in the UK study, so I question the validity of those numbers. How many leukemias and brain tumors would you have had in a similar population that didn't have CT scans when they were --

DR. BERRINGTON DE GONZALEZ: Well, so actually they were

excluded deliberately because we don't think that it's a very good comparison. It's very -- so we have a comparison group instead that is people with very low doses of radiation. So children who had extremity CT scans rather than children who had no CT scans who might be different in some systematic way. And always evidence for getting closer to a causal relationship or causal interpretation of risks is a dose response relationship rather than just ever/never exposed, or had a CT scan/didn't have a CT scan.

So the idea was that the dose response relationship in demonstrating that is actually much better evidence than if we just looked at ever/never exposed because of the potential systematic differences.

DR. DAUER: But it seems the Australian study would have actually been more reliable showing that dose relationship.

DR. BERRINGTON DE GONZALEZ: Well, it's -- it may have -- in this case it looked linear from 0, 1, 2, 3. What they might have seen is that you had the 0 and the 1 -- could actually have been above or below that because of the systematic differences. So it was helpful that they were able to include it, but it wasn't necessarily part of determining causal relationship.

DR. TALAMINI: Dr. Glassman?

DR. GLASSMAN: Two questions, please. One, with the radiation-induced cancers for the CT colonography, did you take into account the latency period of the development of the cancers and the potential life spans? Because for some of the older patients, they would probably have

died of other causes before they ever developed the radiation-induced cancer. That was my first question.

DR. BERRINGTON DE GONZALEZ: Yes, so absolutely. So the risk -- these lifetime risk estimates were adjusted for competing causes of death. And remind me what the first part of it was?

DR. GLASSMAN: That answers the question.

DR. BERRINGTON DE GONZALEZ: Okay. Yeah, it's always adjusted for competing causes of death.

DR. GLASSMAN: Okay. Second question. For the extracolonic cancers for the radiation dose, did you take into account the benefit of the finding of incidental cancers, which were curable, as part of a benefit/risk ratio?

DR. BERRINGTON DE GONZALEZ: No, so we didn't do that.

DR. TALAMINI: Dr. Zhou?

DR. ZHOU: So I have a question about your UK study. So after they have a CT scan and you follow for three years, how do you adjust for visual confounders afterwards? They may have a cancer that would be due to other reasons besides the CT scan.

DR. BERRINGTON DE GONZALEZ: Yeah, so they might -- so a confounder has to be a factor that's related to both the reason for the CT scan and the cancer outcome of interest. So there's actually very few known causes of these childhood cancers. So the ones that we could think about

and that we investigated were Down's syndrome. So Down's syndrome children have an increased risk of certain types of leukemia and might have either more or fewer CT scans. That bit is slightly uncertain. So that's a potential confounder.

We didn't have direct data in the study, but we actually contacted the Down's Syndrome Association, and they said that during the study period, the Down's syndrome children were actually less likely to have CT scans than other children because the CT scans took so long that they would have had to have sedated them. We had only one case of the typical Down's syndrome related leukemia in our study, so we think that that was at least fairly good indirect evidence against confounding by that factor.

In terms of the head CT scans, it's a bit more difficult. I think that whereas -- also we know that head CT scans are performed in -- to assess symptoms that might eventually relate in a cancer diagnosis, so we looked at it in two ways. We did this five-year exclusion period that I showed you that was the standard analysis. We also did a 10-year exclusion period where we only counted CT scans that were performed more than 10 years before the brain cancer was diagnosed. And the dose response relationship was identical.

We adjusted for socio-economic status -- the findings. And as I say, currently there just aren't really other known causes of these cancers that could have been considered or investigated as confounding factors.

DR. TALAMINI: Dr. Steinberg?

DR. STEINBERG: A couple of questions. It goes back to latency. Tell me again, in the children's study with brain cancer, what was the latency between the exposure to radiation and when the data was collected?

DR. BERRINGTON DE GONZALEZ: So we forced it to be at least five years for that main analysis, and then we did the sensitivity analysis where we made it 10 years.

DR. STEINBERG: Okay. And it's not a long period -- that's not 20 years. It's 5 to 10 years. So, how would that compare to -- where would we see cancers? If there were radiation-induced cancers in adults from abdominal CT, from CTC, when would they be? They would be 5 years later, 10 years later, 20 years later.

And a side question -- doesn't it depend on -- do we have data on the sensitivity of different organs in the abdomen? In other words, the pancreas is more sensitive to DNA damage from radiation versus the colon. Or are you treating all the organs equally?

DR. BERRINGTON DE GONZALEZ: So most of the evidence in the studies like the Japanese atomic bomb survivors suggests that five years is the minimum latency for solid cancer, and it's more typically 10 years. So to answer the previous gentleman's -- the other part of your question was about latency. So all these models assume that there is at least a -- it's one of the uncertainties, but at least a 5- to 10-year latency period for solid cancers.

There's differences in terms of the risk per unit dose for say colon cancer versus pancreas. It's higher for colon cancer than for pancreas. But mostly we haven't seen differences in the latency.

So if you -- and we would never know whether any of these cancers were radiation related. Currently we don't have any way to tell the difference between radiation induced and sporadic. But you would expect them to occur at least 5, if not 10, years later. The only difference is leukemia where the latency seems to be much shorter. And that's been shown in children and in adults. And it could be as short as two years.

DR. STEINBERG: And is there any data to suspect that one organ in the abdomen is more radiosensitive to damage than another organ, outside of the bone marrow?

DR. BERRINGTON DE GONZALEZ: Yes, so the -- it appears -- this is again primarily from the Japanese atomic bomb survivors -- the bladder and colon, for example, are more radiosensitive than the pancreas.

DR. TALAMINI: Dr. Ahlgren?

DR. AHLGREN: You've used the linear extrapolation model for cancer risk versus dose, which seems to be the generally accepted model, and from which there seemed to be data down -- from the pediatric studies down into the 100 or maybe even the 50 mSv range. The leading contender with that is the threshold model, which would predict less rather than more cancers as the dose is reduced.

Would it be fair to say then that your estimate of the benefit/risk ratio is actually a conservative one? And if your model were incorrect, it might be even better?

DR. BERRINGTON DE GONZALEZ: Well, that was why I showed that graph from David Brenner's paper, which showed all the alternatives. The linear no-threshold was the red line in the center, and there were several alternatives like the threshold model, which would predict lower risks. But there are some models that would predict higher risks as well, so I would prefer to say that we're in the middle. But certainly if the threshold model turned out to be true, then our risks would be overestimated.

DR. TALAMINI: Dr. Foxx-Orenstein?

DR. FOXX-ORENSTEIN: Do we have any information on effect of CT scan -- I don't know that it exists on CT colonography -- but on fertility?

DR. BERRINGTON DE GONZALEZ: That's an interesting question. No, no one has ever studied it directly. Most of the evidence on fertility is really related to much higher doses, so people who've had radiotherapy 5 Gy to the ovaries and the impact that that has on inducing infertility. But I don't think anyone's looked or could look at these low doses. I presume that that is a risk that has -- well, there is a threshold. I don't know the exact threshold -- rather than it being like cancer where you get risk potentially at any dose, that it was something -- it's a pretty high dose threshold.

DR. TALAMINI: Dr. Isaacs?

DR. ISAACS: With the repeated screening with the CT colonography, would you expect the increased cancer risk to be a linear or do you think -- or greater than linear with the repeated exposures? Because you potentially have a person between the ages of 50 and 60 having three scans.

DR. BERRINGTON DE GONZALEZ: Well, so we think that it's still linear from the studies that I showed you: the tinea capitis study, the repeated breast -- the repeated spine x-ray and the fluoroscopy TB. Again, there was also the estimate of the risk per dose consistent with the atomic bomb survivors who had one single dose at one point in time. So from what we understand, both experimentally and from the epidemiological data, if you have 50 mGy at one point in time, the risk certainly isn't -- so if you have say 100 mGy spread out over 15 years, the risk certainly isn't higher than if you have it all in one dose. If anything, it might be slightly lower because of potential repair mechanisms. There's no reason to think that it should be higher.

DR. TALAMINI: Dr. Applegate.

DR. APPLEGATE: First, I want to commend Dr. Berrington Gonzalez for an excellent presentation. And the research done in the UK study is moderately strong evidence. I mean I think it's very solid and in terms of why other people -- I mean we might ask ourselves why this hasn't been done before. It's a very difficult thing to study.

And I'll just make one comment about the head CT dose and ask you to verify this. If my understanding is correct, the study was performed a number of years -- or looked back at a number of years ago when the doses as far as we understand were much higher than they currently are. So I think if we look at the risk assessment, to your point that you asked the question about whether we are underestimating risk, I think we may be overestimating it, if anything, if we understand the study period.

It was performed looking at doses we were depositing in children in the 1980s and 1990s because the doses that we were using were done using adult doses and not children's doses, and the equipment that we now have is much better than it was at that time. So I think we should understand that and know that the doses we now use today are much lower. Is that a fair statement?

DR. BERRINGTON DE GONZALEZ: Yes, that's correct. The calculations I presented were based on a specific protocol, so they are reasonable for that protocol. But certainly, as it's been suggested, you could use even lower dose protocols probably for the CT colonography, and that would further lower my risk estimates.

DR. TALAMINI: Dr. Charabaty?

DR. APPLEGATE: I was just talking about your head CTs, the head CTs from the surveys that were done in the UK at that time, the estimates that you used in your study.

DR. BERRINGTON DE GONZALEZ: Yes. But then we estimate the risk ultimately per unit dose.

DR APPLEGATE: Right.

DR. BERRINGTON DE GONZALEZ: So that doesn't change. But if you wanted to talk about how those risks transfer to -- for today, then the risk from a single head CT scan to a child is lower today than it was 20 years ago, yes, very likely.

DR. TALAMINI: Dr. Charabaty?

DR. CHARABATY: Thank you again for this presentation. I just want clarification because I got a lost a little bit. In a couple of slides you mentioned that the incidence of radiation-induced cancer was 60 in 100,000. Are these in 100,000 patients undergoing CTC every five years starting age 50 or per 100,000 CTs, whether a CTC or a follow-up CT for incidental finding, or any CT?

DR. BERRINGTON DE GONZALEZ: So the estimate of 60 radiation-induced cancer per 100,000 patients, that was for 100,000 people who underwent one CT colonography each at age 50.

DR. CHARABATY: So just one?

DR. BERRINGTON DE GONZALEZ: Yeah.

DR. CHARABATY: Not the whole screening from 50 to 75 or 80?

DR. BERRINGTON DE GONZALEZ: Well, when I then showed the yellow graph, which shows the radiation risk versus benefits, that is for -- that

is for repeated screening. The only difference there is not every -- although we say we're looking at screening from 50 to 80, not everyone will undergo -- actually undergo screening every five years in reality because they die, or because they have something detected and they go into a different screening protocol.

DR. CHARABATY: So, can you estimate if somebody has at least three or four CTC every five years, what would that risk be?

DR. BERRINGTON DE GONZALEZ: Yes, it's just three times the risk from the single screen.

DR. CHARABATY: Thank you.

DR. TALAMINI: Dr. Steinberg?

DR. STEINBERG: I wonder if you could -- if you're able to tell us about the data and the different way that at least I'm used to hearing about the risk of colon cancer, for instance. So we know that if a first degree relative has colon cancer, it confers maybe 100% -- it doubles the risk of colon cancer.

So if you had a CT colonography, how much increased risk -- what percent risk, if you could put a number on it, over the next 5 or 10 years -- are we talking about 1% more than the general population who didn't get exposed to this? .1%? Do you have --

DR. BERRINGTON DE GONZALEZ: Yeah, so it's -- if we say that the risk is, say to simplify things, 100 per 100,000, then that tells you it's .1%.

DR. STEINBERG: It's .1% over the general population?

DR. BERRINGTON DE GONZALEZ: So you're increasing your lifetime cancer risk from 30%, say, for the general population to 30.1%.

DR. STEINBERG: My last question is are there any ongoing -- it's amazing how little data we have to make these decisions on. We have this -- some pediatric studies. Are there any ongoing studies in adults that are -- will give us firm data on all the diagnostic CTs we're doing on patients?

DR. BERRINGTON DE GONZALEZ: So there's one cohort that has included adults. It's a Canadian study using the Ontario healthcare system. I'm working with them, collaborating with them. We're going to be analyzing the data probably next year. And so, they have children and adults. I think they have about 2 million adults, and they use basically the same design, this retrospective design with CT scans back to the 1980s. We're not certain even with 2 million CT -- even with 2 million adults that we'll have enough power to look at the cancer risks in the adults, but we're certainly going to at least investigate it.

So I'm not sure that I would say that in a year's time there'll be definitive data, but there will be some data. And the question of confounding is also much more complicated when you get into the adulthood cancers and adult CT scans.

DR. TALAMINI: Last question before break.

Dr. Imrey?

DR. IMREY: Just following on Dr. Ahlgren's question earlier, you've rather carefully bracketed the linear dose extrapolation model as an intermediate choice on alternatives. If one looks purely descriptively at the ABCC data that you showed, it appears to be what you described as downward curving in the dose range, relevant to our discussion today.

On the other hand, my question is are there mechanistic and widely entertained biological models that would suggest downward curvature is a viable rationale? I've heard the discussion between the linear low dose and the sublinear extrapolation models for my entire career, but I haven't heard much about this downward curvature model.

DR. BERRINGTON DE GONZALEZ: So I think there's much -- there's less experimental evidence that supports it. There's the bystander effect idea, this idea that if you have some exposure to another part of the body, that somehow the cells communicate and that even unirradiated parts of the body can end up with risk.

So that graph that I showed is from David Brenner's review paper, so it -- I wouldn't say -- you could perhaps draw the thickness of the curves in relation to the amount of evidence that you think there is supporting them. And I would say the upwardly curving one would then be a thinner line than the threshold or the downwardly curving one. But to be open about all the possibilities, I wanted to show them all for this panel.

DR. IMREY: I'm sorry. I'm not sure whether you're reversing

the labeling. I just wanted to clarify. It sounds to me that you're saying that the model that looks like this has perhaps -- taking Dr. Ahlgren's point earlier -- has perhaps less weight of evidence behind it than the discussion between the linear model and the model that's sublinear in the sense of coming down like that.

DR. BERRINGTON DE GONZALEZ: Yeah.

DR. IMREY: Which would, if that is the case, suggest that you're -- that the linear low dose extrapolation that you're using is perhaps conservative to some degree within the scientific spectrum of discussion.

DR. BERRINGTON DE GONZALEZ: Yep, that's correct.

DR. IMREY: Thank you.

DR. TALAMINI: Thank you for a very clear presentation. I again thank the Panel for great questions.

DR. BERRINGTON DE GONZALEZ: Thank you.

DR. TALAMINI: We will now break for lunch. Panel members, please do not discuss the meeting topic during lunch amongst yourselves or with any members of the audience. We will reconvene at 1:00 sharp. Please take any personal belongings with you at this time. The room will be secured by FDA staff during the lunch break. You will not be allowed back into the room until we reconvene. Thank you.

(Whereupon, at 12:00 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:01 p.m.)

DR. TALAMINI: So folks, it is now one minute after 1:00, and we would like now call this meeting back to order, so if we could have the attention of all the Panel members?

We have one more presentation, and then the public comments -- and I would like to remind the Panel members that the goal of this Panel from the FDA's point of view is to hear your expert opinions and our discussion as a Panel on these two questions. And the culmination of this meeting will be two hours in which we will ask each -- or three hours, in which we will ask each committee member -- and we'll want to hear from everybody -- what your opinion is with regard to those two questions.

So as you listen to the remainder of the presentations and the questions and the answers, it would be helpful if in your minds you're beginning to formulate your comments, your opinions with regard to those two questions, which is the ultimate goal of this Panel. And I know you've seen them before. You have them in your packet. They've been on the screen. They'll be on the screen again. But please keep them in mind as we go forward through the remainder of the afternoon. It will very helpful when we get to that three hours of discussion.

With that said, our next speaker is Dr. Ronald Summers, Senior Investigator, Radiology and Imaging Sciences, National Institutes of Health

Clinical Center.

Dr. Summers.

DR. SUMMERS: Thank you very much for inviting me to this session. It's a great pleasure to be here.

These are my disclosures. I do receive patent royalties from a license to iCAD through NIH. And my other disclosures are shown.

So just to put this into perspective a little bit, the scientific activity on CT colonography went through a dramatic phase in the 2000s, peaking around 2009 or 2010. And now it's in what I would regard as a more mature phase of development where focus is on some of the larger clinical trials that you've heard about today. So while the number of publications have been falling, the focus has definitely been on these larger trials.

Now, my purview in this presentation has -- as you can see from this overview is to serve as sort of a cleanup hitter to kind of cover all kinds of different topics. And I'll do my best in the time allocated to cover these different areas. I'll discuss some other recent clinical trials besides what we've already heard today. I'll describe a meta-analysis on colorectal cancer detection. I'll talk about extracolonic findings, 6-9 mm lesions, and flat polyps. I'll discuss some data on performance in the Medicare population, data on patient acceptance, and finally, technical improvements and computer-aided poly detection, or CAD.

So the first segment of this will be about clinical trials, and the

first trial that I'll discuss is one conducted in the Netherlands by Stoop et al. published last year in *Lancet Oncology*. They were looking at screening patients. And the structure of this trial was to invite patients in the community to either CTC or optical colonoscopy and to ascertain several things including: the participation rate, in other words what fraction of the people invited actually came and got the screening test; the advanced neoplasia rate per participant; and then the advanced neoplasia rate per invitee.

And in this particular study there were 982 patients in the CTC arm, 1276 in the OC arm. The participation rate for CTC was about 50% higher than for OC -- 34% versus 22%. The advanced neoplasia detection rate per participant was about one-third higher for OC -- 8.7 versus 6.1%. However, when you took into account these two factors, participation rate and advanced neoplasia detection rate per participant, the product of those is the advanced neoplasia rate per invitee. And you can see that these were roughly 2% and not statistically significant. The cancer detection rate per participant and the cancer detection rate per invitee were also not significantly different.

The second trial I'll discuss is a trial in Germany referred to as the Munich trial. This trial led by Anno Graser and colleagues was published in *Gut* in 2009. There were 207 participants who underwent both CTC and optical colonoscopy. And the performance of flex sig was simulated in the

optical colonoscopy patients by just looking at the rectal and sigmoid findings of the optical colonoscopy.

The advanced neoplasia sensitivity and specificity per patient were comparable for CTC and optical colonoscopy and slightly lower for flex sig. The advanced neoplasia specificity per patient was around 39 to 43% for CTC and OC, and a little higher for flex sig. The sensitivity and specificity for adenomas greater than 9 mm were comparable for CTC and optical colonoscopy. Sensitivity was lower for flex sig. And for adenomas greater than 5 mm, again, sensitivities and specificities were comparable for CTC and optical colonoscopy, sensitivity lower for flex sig.

Another finding of interest in this particular study was that the per polyp sensitivities, while they were similar for both OC and CTC for adenomas and advanced neoplasia, in one category OC was more sensitive, and that was for 147 adenomas less than 6 mm. Where the sensitivity is much higher for OC, just keep in mind, of course, that with the structured reporting, those smaller lesions are generally not reported.

The third study I'll talk about is one from the Massachusetts General Hospital on laxative-free CTC. There were 605 patients in this study. The sensitivity and specificity were high, 91 and 85% for the larger polyps, and sensitivity fell as the polyp size threshold went down. And one of the reasons for that is that this laxative-free evaluation of CTC is more difficult because of the presence of residual tagged stool, which is a different

situation than that for the ACRIN and DOD trials that you heard about earlier. While I'll talk about patient experience in more detail later, the patient experience was better with the laxative-free CTC compared with OC.

The second topic is colorectal cancer detection, and this is my summary of a meta-analysis from Dr. Pickhardt and colleagues. They looked at 49 studies on over 11,000 patients. There were 415 cancers or a 3.6% prevalence. So, clearly, this includes not just screening patients, but also diagnostic patients. The CTC sensitivity for colorectal cancer was 96.1%, and that compared favorably with the 94.7% sensitivity for optical colonoscopy, which was reported -- OC results were reported in 25 of those studies.

The conclusion of this paper was that CTC and OC should be considered equivalent in terms of sensitivity for colorectal cancer detection and may be complementary.

I'm now going to switch gears and talk about extracolonic findings. So we've already seen this chart from one of the earlier speakers, and I'm going to focus just on the E score. You'll recall that the C-RADS guidelines have a C score and an E score. The C score is the colonic findings. The E score are the extracolonic findings.

And the papers that have looked at extracolonic findings have focused mainly on the E3 and the E4 lesions. These are the likely unimportant findings that are incompletely characterized, such as minimally complex or homogeneously hyperattenuating renal cysts, or the potentially

important findings such as masses in different organs.

Not to belabor the obvious, extracolonic findings are findings outside the colon. These are things that would not be seen at optical colonoscopy. The concern is that these are commonplace, and some require workup, but they can lead to a benefit for patients, particularly with large abdominal aortic aneurysms, renal masses, lung nodules, lung cancers, lymphadenopathy, and to a lesser extent ovarian masses. Those generally tend to be benign.

So let's look at some of the extracolonic findings workup rates reported in several studies. And this is data that I adapted from a recent paper of Judy Yee's and *AJR*. I've listed five different studies with the number of patients in each study, the workup rate, and the number of extracolonic cancers that were reported in those studies.

The workup rate is the number of patients who went onto either additional imaging or intervention because of an extracolonic finding at CTC. And these workup rates ranged from a low of 5.5% to a high of 49.9%. And as Dr. Yee pointed out in her article in the two studies, the bottom two, from Kimberly and Park, those investigators did not use structured reporting or C-RADS in which management guidelines are given on how to respond to different extracolonic findings, and that likely is the reason behind these high workup rates in those two studies. And the number of extracolonic cancers ranged -- additional extracolonic cancers ranged from 0 to 7 in the studies

that reported that data.

I'd like to mention some other things that haven't been reported earlier in many papers. That is the possibility to do simultaneous screening for other diseases with CT colonography. These are concepts that are just recently undergoing scrutiny. For example, one can screen for osteoporosis without any additional radiation exposure by measuring bone mineral density in the spine, such as in this example where we can measure the bone mineral density in the vertebral body in the spine.

And in this paper from the *Journal of Bone and Mineral Research* where CTC bone mineral density measurements were compared to DEXA or dual x-ray -- dual-energy x-ray absorptiometry experiments that a threshold for density of the bone marrow could be given at 160 Hounsfield units for identifying nearly 100% of patients with osteoporosis.

And, similarly, it's also possible to assess for visceral fat. And we showed in a study of the DOD patient cohort that the patients with the highest amount of visceral fat, shown here in blue coloring, had about twice the odds of having polyps compared to the thinnest patients. So that's another opportunistic thing that can be done with CT colonography is assess for visceral fat, which can be associated with metabolic syndrome, another important disease entity.

Now I'll switch gears and talk about 6-9 mm polyps, as these have drawn considerable attention in the literature. And what I found very

interesting about the discussion about 6-9 mm polyps is that it really is a tradeoff. It's a tradeoff between the referral rate for colonoscopy, as shown by the cyan and yellow line here from the ACRIN trial and the DOD trial, versus the risk of high-grade dysplasia or cancer in polyps, as shown in these four other curves, from an older paper by Muto and a more recent paper by Lieberman.

And so, one of the concepts in CT colonography is that it might be possible to have patients with 6-9 mm polyps in this range undergo surveillance to see which polyps would grow and hence identify the polyps that really needed to be removed rather than just remove everything with the additional potential for complications that that involves.

And this very interesting information about the 6-9 mm polyps is underlined by this recent work that just came out within the last month or two in *Lancet Oncology* from Dr. Pickhardt and colleagues looking at polyp volumetric growth rates. With CTC it's possible to measure the volume of a polyp, not just its linear size. And what the investigators did was they measured the volume of all the polyps and the correlated volume change over time. As these patients were in a surveillance population and had serial CTC examinations, they could measure volumetric growth rates.

And what they found was that advance adenomas could grow an average of 77% per year, whereas other types of polyps either grew very little, remained relatively stable in size, or even got smaller. And this led to

the investigators stating that once a polyp reached a certain size threshold, there was a very high sensitivity for identifying that particular polyp as an advanced adenoma, which some regard as one of the main targets for a colorectal cancer screening.

So in this graph I show an analysis that I did of this data from the *Lancet Oncology* paper showing what would happen if we did watch polyps in a surveillance population. Let me help you understand this graph. So the dark blue horizontal line at 6 mm is the C-RADS reporting threshold, so we don't report polyp smaller than that. The red line is the 180 mm^3 equivalent volume at which the investigators in the paper I just mentioned stated that nearly 100% of advanced adenomas could be detected. And these light blue, green, and purple curves show how large polyps would get at the average size of 77% annual growth for an advanced adenoma. And these would be the growth rates at the extreme upper and lower ends of the confidence intervals.

And the bottom line of all this is that there's about a two- to three-year interval between when a polyp reaches the C-RADS reporting threshold and when it reaches this high sensitivity threshold for identifying advanced adenomas. So this is the sort of data that will be very important going forward at determining what surveillance intervals should be and also whether we -- at what size threshold we should really be removing polyps, an area that I think is really ripe for future research.

Okay. I'm going to switch now to flat lesions. So flat lesions have generated a lot of interest because they're harder to see at both optical colonoscopy and CTC. One of the challenges that we've had in the research community is the lack of a uniform definition of what a flat polyp really is. In this review article in *Abdominal Imaging* a couple of years ago, the authors concluded that the incidence of flat adenomas and carcinomas was low and that most could be detected by CTC, and that fecal tagging, 2D and 3D image interpretation, and computer-aided detection might help.

In this paper in *Academic Radiology* several years ago from the Wisconsin group, about 13% of 954 polyps were classified as flat, such as the one shown in this image from their paper. Compared with the non-flat polyps, the flat polyps were less likely to be adenomas, histologically advanced, or malignant. You can see the difference is quite substantial for adenomas, and that was statistically significant for histologically advanced polyps, whereas the difference is numerically large that just missed reaching statistical significance. And the difference for malignancy did not reach statistical significance.

Okay. Now I'll switch to performance in the Medicare population. So as was alluded to earlier, the interest in this topic arose from the CMS review of CTC for the question of reimbursement and led to several retrospective analyses of existing data from the major trials.

The ACRIN trial reported its results in the Medicare population

just a year ago. This table summarizes the data for large adenomas and cancers for which both the sensitivity and specificity were not significantly different. Similar conclusions were drawn for the 6-9 mm polyps where the sensitivities were lower. But, again, differences were not statistically significantly different comparing the senior versus the non-senior population.

Other factors looked at in these later analyses of the Medicare population included looking at advanced neoplasia prevalence in the senior and non-senior population. The prevalence of advanced neoplasia tended to be higher, except in a paper by Macari and colleagues where it was the same. So there's about twice as much advanced neoplasia in the seniors. In the Kim et al. experience and the ACRIN reanalysis, advanced neoplasia prevalence of 3.3% was reported from the Colon Health Initiative, although not comparable data for this particular paper.

The optical colonoscopy referral rates tended to vary. They tended to be a little lower for the non-seniors than for the seniors in the Kim et al. paper. They were comparable in the Macari et al. paper. In the ACRIN reinvestigation they did not report separate OC referral rates, but the referral rate for both seniors and non-seniors was reported to be 12% in the original paper. So from that one can infer that it's probably similar between these two groups.

Now, let's look at the extracolonic findings in the Medicare population. There were four papers that presented some data on this. The

number of patients in these studies is given here, and the percentage of patients with either E3 or E4 C-RADS findings are given. These first two papers listed the EC workup rates from 2.4 to 7.8%, which was comparable to the non-senior population. The other papers did not report EC workup rates for the senior population. The ACRIN trial did not collect data about EC workup rates. And, finally, extracolonic cancers in the senior population, one was reported, but also 18 abdominal aortic aneurysms in the Wisconsin paper.

Okay. I'll switch gears again, and we'll talk about patient acceptance. These are typically done by questionnaire, frequently by giving patients questionnaires after the examination is done, either immediately following or at some period after the examination. These five papers present data from various groups of patients.

The Pooler data included data from an academic center, a DOD center, and an outpatient center. The Stoop paper -- rather than preference, I'm reporting the participation rate here as a surrogate for that as they did not report preference. Moawad, I believe, was from DOD. Graser is from that Munich trial. This is from the original DOD trial. And you can see that the gap in CTC preference compared to OC preference is much smaller in the Munich trial than in the other trials. However, all of these differences were statistically significant.

What were some of the reasons that patients preferred CT

colonography over OC? I'm showing a list of such preferences from the Pooler paper, although this list is fairly common across different investigations. These include: non-invasiveness of -- relative non-invasiveness of CTC; the avoidance of sedation or anesthesia; the ability to drive oneself after the test; the avoidance of colonoscopy risks such as perforation; the ability of CTC to identify abnormalities outside the colon; and the ability to return to work immediately after the test.

This paper from Lin et al. in the *Journal of General Internal Medicine* published last year was a meta-analysis of patient preferences comparing studies that looked at diagnostic patients and screening patients. So today we're focusing on screening. That's the lower third of these studies. And you can see that on balance this graph shows the difference in the preferences for CTC versus colonoscopy. So, in other words, if you subtract the number of patients that preferred CTC from the number of patients that preferred colonoscopy, that's what's shown here. And on average, which is this last bar -- this last data point here, just over 50% of patients tended to prefer CTC in the screening papers.

Those of you who are perceptive may ask why some of these papers were not included in my mention of clinical trials earlier in this presentation. And that's because some of these trials included patients at high risk for colorectal cancer, so I did not include them for that reason. Since I have the data on the screen, I'll just mention that for diagnostic

patients, the preference for CTC over OC was not statistically significantly likely because the patients had a much higher probability of having colonic findings and a higher probability of needing to get a colonoscopy anyway.

Okay. The next topic is technical improvements. And one of the things that CTC is amenable to is a number of improvements that -- technical developments that leverage its digital image quality. And this includes doing things like supine-prone registration, optical colonoscopy polyp location prediction, and electronic stool subtraction for the laxative-free bowel prep.

The group at the University College London recently published a really great paper on showing how the supine and prone CTC scans could be exquisitely registered by flattening the colon and then morphing this flattened view so that the polyps could be registered exquisitely so that when the fly-through -- the synchronous fly-through is done, as shown very nicely in Dr. Barlow's presentation, the colons can be rotated and aligned longitudinally into exquisite alignment so that if there is a polyp in a particular location, it'll be seen in the exact same place on the image, leading to improved diagnostic confidence, whereas stool might not tend to be in exactly in the same position. So this is a technique which is not yet available clinically but could easily be implemented.

Another registration that may be helpful is to register the CTC to the OC so that if a polyp is found at CTC, its location can be precisely

predicted on the OC. And we heard in the earlier presentation that sometimes optical colonoscopy can't find a polyp found at CTC, but then on a follow-up CTC, a polyp is again identified in the same place and ultimately identified on OC. In part, that may be because of the difficulty of knowing precisely where to look. And this technique uses the physical properties of an optical colonoscope to deform the CTC image into the shape of the colon that would occur during the OC, and that way register the CTC to the OC more precisely and lead to identification of the majority of polyps to within one colonoscope mark or less. The colonoscopes have marks every 5 to 10 in centimeters for longitudinal guidance.

Laxative-free bowel prep is something that I mentioned earlier in one of the clinical trials. This typically utilizes electronic stool subtraction. Here tagged with iodinated contrast material are several pieces of residual fecal matter, and using electronic stool subtraction, these piece of feces can be removed electronically from the image and then enable improved depiction of the colonic wall and polyps. And in a study, we reported it leading to a 10 to 15% increase in sensitivity for detecting large polyps. That's something on the horizon.

The next topic is computer-aided polyp detection. Back in 2005, using the DOD data set, we reported in *Gastroenterology* a CAD system that had a per-patient sensitivity that was comparable to that of optical colonoscopy for adenomas 8 mm and greater. This should be greater than or

equal to 8 mm. And this is a polyp at OC, at CTC, and this blue mark is the CAD mark indicating the polyp.

Following that study, there have been a number of investigations from different groups looking at how CAD might be used in the clinical setting. These studies can be divided into those looking at different reading paradigms known as the first read, the concurrent read, and the second read.

Briefly, what these are is the first read means that the physician only looks at the CAD, not the whole scan, and makes their diagnosis based on just the CAD findings. The second read is a scenario where the physician reads the entire scan, makes a diagnosis, and then looks at the CAD findings and revises their diagnosis. And, finally, the concurrent read is an intermediate type of read where the CAD marks are incorporated into the CTC images, and the physician sees them as he or she is interpreting the CTC.

So let's look at how well the CAD operates in these different scenarios. This is a group that reported in *Radiology* this year the use of CAD in the first read mode and compared it to a double reader mode and found that per polyp sensitivities for all the different reading modes were similar and very high ranging from 88 to 89% for per polyp. And one of the main benefits of the first read was as very short reading time. They reported about 100 seconds to read a case, if the number of CAD prompts was less than 10 per patient.

This is a paper by Dr. Dachman and colleagues reported several years ago with a CAD system in which -- that was used by 19 radiologists on 100 cases. They found that CAD improved the area under the ROC curve, and the per-patient and per-polyp sensitivities. There was 8% increase in sensitivity for detecting small adenomas and a 2.5% decrease in specificity.

The UCL, the University College London group, reported a second and concurrent reader CAD study looking at 16 radiologists reading 112 cases. They found that second read CAD significantly improved readers per-patient and per-polyp detection, but concurrent CAD was less effective. These images from their paper show the reader sensitivity and specificity for the different readers. On the left is the second read CAD. On the right the -- I'm sorry. Yes, the second read CAD, on the right the concurrent CAD, and the red mark shows the average of all the readers' performance. And there was a statistically significant increase in sensitivity of about 8%, whereas there was not a statistically significant increase with the concurrent CAD.

So to conclude my remarks, the recent trials show comparable sensitivity and specificity between CTC and optical colonoscopy. The colorectal cancer sensitivity and specificity are very high, according to the meta-analysis that I showed. The extracolonic findings are well understood and their management elucidated according to the C-RADS guidelines. The detection of 6-9 mm polyps by CTC is lower, but I think we need to know about the practical significance of such polyps given what is known about

polyps' growth rates and time to invasive cancer. Flat polyps are uncommon and less likely to be advanced neoplasms. The performance is similar for most measure for senior and non-senior screening populations for CTC. Screening patients tend to prefer CTC over OC. Technical developments may improve the accuracy and enable a more patient-friendly exam, particularly if the laxative-free prep is available. And CAD improves performance.

Before I conclude, I'd just like to add one comment in response to one of the questions earlier, which was about perforation rates. Someone asked about perforation risk in seniors. In the ACRIN trial, there were two severe complications. One was a perforation after polypectomy and one was an E. coli bacteremia that followed both the CTC and the optical colonoscopy.

Okay. So that concludes that remarks, and I'd be happy to answer any questions.

DR. TALAMINI: Could we please put Slide 36 back up just so that that's front of the Panel as the summary slide? Thanks.

Questions from Panel members? Yes, sir?

DR. ZISKIN: I have a question about the electronic stool extraction. Is it possible that that could be effective enough so that bowel preparation would not be necessary?

DR. SUMMERS: Well, that's certainly our hope. The only data so far is the Salas trial -- actually I believe the Dutch trial also used the laxative-free prep. So there is some data that it may be possible to do CTC

without the laxative, but that's still early days I think.

DR. TALAMINI: Dr. Imrey?

DR. IMREY: I wonder if you would clarify the reference standard against which sensitivity and specificity were judged in the Munich trial that you discussed at the outset?

DR. SUMMERS: Right. So they did optical colonoscopy and they did segmental unblinding.

DR. IMREY: Thank you.

DR. TALAMINI: Dr. Dauer?

DR. DAUER: When you were talking about the performance in the Medicare population referring to the Johnson study, you showed that the sensitivity in under age 65 was 92% and over age 65 was 82%. That was a big difference in the Medicare population. Did that explain that perhaps related to the elderly was not able to have a better bowel prep? Or were there reasons why the detection rate was smaller in the older population?

DR. SUMMERS: Okay. So first of all, that difference while numerically perhaps large was not statistically significant. I think there were some comments about distension and bowel cleansing, but I can't remember the details.

DR. TALAMINI: Dr. Pinsky?

DR. PINSKY: You showed the slide with the 6-9 mm in the growth, and I'm wondering -- we sort of have a standard protocol now that

it's -- you report everything that's 6+ and you have a five-year frequency. And I'm wondering is that because you have somewhat lower sensitivity for 6-9 with CTC than OC or because you have presumably low sensitivity for the less than 6 and you're not reporting those at all? I mean what would be able to move the CTC to the same 10-year interval as OC, which would in terms of resource utilization make it a lot more useful?

DR. SUMMERS: Right. Right. So that's a great question, which I think the data from *Lancet Oncology* that I showed would take us along the path to answering questions like that. My understanding is that the five-year surveillance interval was chosen to be a conservative interval, because at the time C-RADS guidelines and these surveillance concepts were developed, CTC was in its early stages and we didn't have as much data as we wanted. So a screening interval comparable to that perhaps for barium enema.

Could CTC screening intervals be lengthened to 10 years? I think with more experience with the test, we might be able to do that. At the time being, I don't think we have data that would bolster that move.

DR. TALAMINI: Dr. Zhou, did you have a question?

DR. ZHOU: So the slides you showed the performance in the Medicare population -- the difference is 10%, and then you were saying it's not statistically significant. And I was surprised because these numbers are so big, if the standard deviation is big, that's the reason they're not statistically significant. The 10% is pretty high in sensitivity. Do you recall?

DR. SUMMERS: Well, the -- I'd have to look at the slide about what the n was for the number of seniors.

DR. ZHOU: N is -- one is 2,000 and one is 477.

DR. SUMMERS: Right. Right. Well, you know, at --

DR. ZHOU: That's a pretty big sample --

DR. TALAMINI: Slide No. 20. If we can bring up Slide No. 20, please?

DR. SUMMERS: Remember it's the number of patients with polyps in the large size category. That's part of the confidence interval calculation, so I don't off hand know the numbers for those patients. You'd have to look at the paper itself.

DR. PINSKY: You can't --

DR. TALAMINI: Dr. Pinsky, go ahead and use the microphone and state your name.

DR. PINSKY: I think that n is not the number that sensitivity is calculated on. It's the total number in the study, right? So the sensitivity is calculated on probably a number smaller n who had the large polyps

DR. SUMMERS: Right. Right. That's the fraction of patients that had a 10 mm or larger adenoma or cancer. So the 10% sensitivity difference has -- the error bars on that have to be computed using the number of patients that have large adenomas or cancers, not the number of patients in the entire study.

DR. ZHOU: So the sensitivity here is polyp sensitivity or the per-patient sensitivity?

DR. SUMMERS: I think these are per patient, but the per polyp data was comparable.

DR. PINSKY: I mean it's per patient, but let's say of the 477, maybe only 10% had a large polyp, so it's 47 is the denominator for sensitivity. Something like that.

DR. ZHOU: Okay. Yeah, but it kind of looks weird.

DR. TALAMINI: Dr. Steinberg, a question?

DR. STEINBERG: I have a couple of challenges here. When I look at the slides you have on patient acceptance, it looks like patients would prefer or accept a CTC over a colonoscopy. But, correct me if I'm wrong, all these studies come from studies where the patient was expected to have a colonoscopy right after a CTC, pretty much on the same day. They were prepared for this sort of sequence.

And if that's the case, when you translate that to real life, when you offer a patient one versus the other -- if I tell a patient, okay, you could have a colonoscopy and we could take your polyps out at the same time versus a CTC where if you go through the CTC you have do to a prep, you -- 10, 15% of the time you're going to have to undergo a colonoscopy after that with a second prep on a second day, usually, in most situations, 10 or 15% of the time they're going to find something on the CT, which will lead to -- an

extracolonic finding, which will then lead to multiple x--rays, only rarely of which will lead to a lesion that's clinically important, and your insurance may not pay for it, when you add all that up and you do a study of patient acceptance of one versus the other, I bet you're going to get exactly the opposite results as these kind of findings.

Because this leaves you with the impression that, well, if you offered it to your average person, this versus this, there's going to be more patient acceptance of CTC. And in point of fact, when you factor all these things in -- of course, we'll have to tell them our perforation rate is 1 in let's say 1500 or 1 in 1,000, and there's 1 in 20,000, so that's got to be factored in too. So, I think it's a lot more -- I think it's kind of misleading to translate this into the real world. And I have another challenge after you --

DR. SUMMERS: Sure. Okay. So just to get at your points, first of all, not all the studies -- not in all the studies did patients have to undergo both tests. For example, the Colon Health Initiative, not everybody is still undergoing both tests. It was only in --

DR. STEINBERG: But most of them were -- I mean they were offered that. They were going to not lose time. It's going to -- same prep. You go from one unit to another unit. Or most of them --

DR. SUMMERS: Well, the issues that you raised about the advantages and disadvantages of the CTC, these are presented to the patients. My understanding is that when these questionnaires are

administered, they provide data to the patients about what the characteristics are of both tests and what the potential advantages and disadvantages are. So all those things that you mentioned are presented to the patients. How they --

DR. STEINBERG: Are you sure of that? All the things that I just listed?

DR. SUMMERS: Well, I have to actually have them all in front of me and scrutinize them carefully to make sure, but --

DR. STEINBERG: Yeah, because I wonder.

DR. SUMMERS: But if they didn't present all the data, that would lead to a poor quality study that would certainly be under quite a bit of scrutiny during peer review. I think if it was that biased that they just left off obvious information -- educational information to the patients, that that would be readily picked up. And I'm sure you'll hear about that in the public comments about deficiencies in these patient preference studies.

So I take your point that they're -- how much sense do we make of patient preference studies? But, nevertheless, this is what it is, and this is the information that was gleaned from this particular study designs.

DR. TALAMINI: Your second question, Dr. Steinberg?

DR. STEINBERG: Yeah. And that is the conclusion that flat polyps are less of a problem than non-flat polyps. That seems to go contrary -- especially flat polyps on the right side of the colon are a big problem. And

so, I wonder about my other GI colleagues -- that's contrary -- we are very concerned about the -- I mean they're not adenomas or they're classified in different ways. And we used to call a lot of the biopsies hyperplastic, and now they're called serrated adenomas.

So I'm wondering is this up-to-date data with the current thinking of flat-sided right polyps that are not called adenomas or -- they're called serrated -- because it's contrary to my understanding of the concern of right-sided flat polyps.

DR. TALAMINI: Could I ask to put Slide 36 back up for us please, sir? Slide 36?

DR. SUMMERS: So while he's putting up Slide 36, I'll try to respond to your comment. So the issue of flat polyps has been one of great interest to the CTC research community, particularly after papers like Soetikno, I think that was in *JAMA* perhaps about -- and there's been some difference in the reported frequency of these flat lesions in the colonoscopy literature and in the CTC literature.

I can only report the data that I found about flat lesions. The Wisconsin group has a lot of experience detecting these flat lesions, and they're saying that they can detect them and that they have a lower incidence of this -- of bad histology. And it is what it is. I hear what you're saying, but this is what the data -- this is what data we have at this time.

DR. TALAMINI: So, in the interest of time, we have two more in

line for questions. Then we're going to need to move along.

Dr. Kelsen?

DR. KELSEN: It's my impression that most of the data that you've presented and we've heard before are people who are already coming for some kind of surveillance, some kind of screening procedure, referred by somebody, and they're willing to get screened.

Is there any data on CTC in populations that you generally can't get to come for some kind of screening procedure? Does it attract people who otherwise wouldn't get anything done, since that seems to be one of the big problems?

DR. SUMMERS: Right. So health disparities has been an important area. There was one study looking at people in an underserved population who would not come for screening -- and it was a questionnaire-based study -- to find out what would get them to screening. And the result of that particular study was that if they were given CTC, they would come and get screened, but then the next thing they said was that if it cost more than $100, I won't come and get it. So there are lots of issues in getting underserved populations into the screening situation.

DR. KELSEN: There's no actual data. The most there is that you know of is a questionnaire that -- would you come if you -- if X or Y was available? But there's not actually -- I'm just asking -- there's not actually a study in which they went to some area that people don't get screened and

they say here it is, and it's free or whatever the heck it is, and they actually did it, and then you could measure the acceptance rate. That doesn't exist?

DR. SUMMERS: Well, some of that data has been hinted at in various studies where participation rates, for example, are higher in the CTC population. And so, one infers that more people would be coming in and getting screened. But the precise data that you're asking, the one that comes to mind is a questionnaire and not an actual clinical trial.

DR. KELSEN: My impression is that those people were coming for a screening procedure in most of these studies.

DR. SUMMERS: Well, no. The Dutch trial they sent letters out, so the people did not come of their own volition to get screening. They were sent a letter, and they either responded or they didn't respond.

DR. TALAMINI: Dr. Foxx-Orenstein?

DR. FOXX-ORENSTEIN: Thank you. I wanted to reinforce what Dr. Steinberg had mentioned about flat polyps being a significant concern to gastroenterologists, particularly right-sided lesions and serrated adenomas, something we're all concerned about and making sure that preps are as high quality as possible. And a lot of discussion has to happen with patients about the quality of the examination reflects the quality of the procedure itself.

Also that Dr. Barlow earlier had commented in response to Dr. Charabaty regarding serrated adenomas and flat polyps, that this was the Achilles heel of CTC. That's all.

DR. SUMMERS: Okay. So you want me to respond to that?

DR. TALAMINI: Yes, please.

DR. SUMMERS: So, in response, let's think about the paper in the *New England Journal* from the Wisconsin group where they compared advanced neoplasia prevalence in parallel groups of patients that underwent OC and CTC, and they found nearly identical adenoma prevalence rates. Maybe CTC didn't perform better at that measure than OC, but it didn't perform worse. So if the question is -- relates to the ability of CTC to find lesions that OC finds, in that particular study that would suggest that it does find them at comparable rates.

DR. TALAMINI: Thank you, Dr. Summers.

We're going to need to move on to the next portion of the meeting, which is the Open Public Hearing.

Welcome to the Open Public Hearing. For each speaker, please state your name and your affiliation, if relevant, to this meeting. If you have any financial interests relevant to this meeting, such as a company's or group's payment of your travel or other expenses, FDA encourages you to state the interest as you begin. If you do not have any such interests, you may wish to state that for the record. If you prefer not to address financial interests, you can still give your comments.

Nine speakers are registered for today's hearing. We have asked you all to limit your remarks to 5 minutes. The yellow light will come

on when you have 2 minutes remaining. When the red light comes on, please close and stop your remarks, and I will likely help you to do so in the interest of time.

Our first speaker is Dr. Judy Yee, Chair of the ACR's Colon Cancer Committee, American College of Radiology.

DR. YEE: Good afternoon. And thank you for the opportunity to speak on behalf of the American College of Radiology, representing close to 35,000 members.

In the 5 minutes that I have -- and I'm going to chew probably 5 seconds talking about this -- I'm going to talk about the ACR perspective on CTC radiation risk, the very low risk of perforation related to CTC, the establishment of our CTC national registry, which is a tool that's used for monitoring quality and safety, in conjunction with the ACR Dose Index Registry. Additionally, I'll talk a little bit more about the validation trials in the senior patient cohorts, which you've already heard about. I'll go through them quickly.

So to start off with, this is from the Brenner paper, who established that the potential lifetime radiation-related cancer risk from CTC was low at .07% to .15%. Of note, as you've heard, this is extrapolated risk from A-bomb survivors, noting that the A-bomb survivors did receive much higher doses of 20 mSv and even much higher than that. And this was using the linear no-threshold model. As we know, this overestimates risk for CTC

since the A-bomb data included children in the calculations and whole body radiation exposure. So the conclusion from this paper was that the benefits of CTC clearly outweighed the risks.

Additional major differences between CTC risk and A-bomb data, if you look at this graph of the age at time of the CTC study versus estimated lifetime attributable risk of death from cancer, you'll see that the rates of cancer induction fall off dramatically after the age of 35 years. And as we know, CTC is proposed for screening starting at the age of 50. Only the abdomen and pelvis and a very small portion of the lung bases are exposed in CTC, so the lungs typically -- the majority of lungs are not radiated, and lung cancer is one of the primary cancers thought to be caused by radiation. The radiation dose for CTC is much lower. You've heard at 7-8 mSv compared to the 20 mSv and much higher with the A-bomb survivors.

This was a study comparing radiation dose of CTC versus double-contrast barium enema. And from this paper you can see that the effective dose of CTC was at 2.17 mSv, certainly lower than the 3 mSv bar that we've not set. The effective dose of double-contrast barium enema was close to twice that of CTC.

This was a study looking at the trends of radiation dose for CTC. And you can see that out of 109 institutions, 62 responded. The medium effective dose was at 4.4 mSv. They decided that this was not significantly different compared to a 2007 study at 5.7 mSv, but certainly trending

downward. It was noted, though, at the same time that at 4.4 mSv, this is about half that used in the modeling study by Berrington de Gonzalez. So this should result in even higher benefit-to-risk ratio than predicted in that study. This is pulled off of my CT scanner -- I work at the San Francisco VA -- and you can see a close to 60% reduction in dose.

Let's talk about perforation risk. So, if you look at CTC, the total -- this is from the Pickhardt trial -- is at 2 in 22,000. This compares to 1 in a 1,000 for diagnostic colonoscopy.

DR. TALAMINI: You've got about 60 seconds.

DR. YEE: Okay. Talk about the NRDR. The National Radiology Data Registry was established to compare site performance to regional and national benchmarks. Sites can then target specific areas for improvement and then implement quality assurance measures. Sites can also document quality to payers. We have over 5,900 patients registered.

These are the measures. You can read them off. Adequacy of bowel cleansing distension, technical adequacy, perforations, true positive rate, and significant extracolonic findings.

Here's a sample benchmark report. I'm not going to have time to go through this, but you've already heard the results.

And in conclusion, CTC is validated as an effective safe screening test. The benefits outweigh the radiation risks. Current techniques decrease dose by 50-60% to 3 mSv and below, equivalent to annual

background dose. Perforation is much lower. And, of note, there are no deaths ever reported due to CTC. And the ACR CTC Registry is in place for continued monitoring of CTC quality and safety. Thank you.

DR. TALAMINI: Thank you, Dr. Yee. I appreciate your timeliness.

Next is Brandel France de Bravo from the National Research Center for Women and Families, Cancer Prevention and Treatment Fund.

MS. FRANCE DE BRAVO: Hi. Thank you for allowing me to speak here today.

Our center, non-profit center analyzes and reviews research and provides objective and understandable health information to patients, healthcare providers, and policy makers. And we don't accept funding from companies that make medical products, so I have no conflict of interest.

Five points stood out to me after reading the FDA summary and also hearing everybody's questions and the presentations today. It's pretty clear there's no one method of screening asymptomatic patients that meets the three necessary criteria for increasing compliance. That is, that the method be highly accurate, very low risk, and involve little to no discomfort, either physical or psychological, and by that I'm including the yuck factor.

Optical colonoscopy has not been as widely embraced as many health experts would have liked, except perhaps by some unscrupulous surgical centers, which the *New York Times* reports are charging insurance

companies as much as $6,000. The *Times* has also noted that colonoscopies are "the most expensive screening test that healthy Americans routinely undergo," often costing more than childbirth or an appendectomy in most other developed countries. So while it has its downside, it does offer, as we've heard, a two-for. That means it screens patients for colon cancer, but of course it also removes potentially pre-cancerous polyps all in one go.

Now, virtual colonoscopies don't screen and treat. They just screen, which is why the term virtual colonoscopy is kind of a misnomer. But it is a great marketing tool as it implies a clean, no fuss, no muss approach. In fact, patients still have to go through the grueling process of bowel preparation.

Now, CTC isn't as good as optical colonoscopy at detecting polyps or lesions of 10 mm or smaller, as we've heard. Maybe that's not as important given that polyps over 10 mm are less likely to be suspicious and in need of removal. But, again, we need more research. It's somewhat reassuring that the smaller ones seem to sometimes shrink and disappear on their own. That's good.

Now, while CTC is less sensitive for smaller lesions and exposes patients to relatively high doses of radiation, it does offer one major benefit over colonoscopy. It reduces the major risk of bleeding and disease transmission, both of which are a particular concern in older patients. So that's on the plus side.

Besides exposing patients to radiation and missing smaller polyps, CTC opens a Pandora's box of extracolonic findings. These are suspicious findings in nearby organs. Now, these can lead to more diagnostic tests, some of which may be invasive or harmful, but they also sometimes save lives.

Now, while radiologists often dismiss worries about excessive exposure radiation, our Center continues to be concerned because so many patients are being exposed to radiation from so many different medical tests, as discussed by Dr. Berrington.

There are a couple of safeguards or pieces of information that I would like see discussed. First off, I think we need to know -- Dr. Summers presented interesting information about patient acceptance, which was a big concern of ours. Before going full speed ahead on anything, we want to know is this really going to make a difference.

Unfortunately, questionnaires after procedures, as one panelist raised the question -- questionnaires after the procedures are not the same thing as actually having a head-to-head test, which would really measure what patient acceptance is all about. And that's the purpose of patient centered outcomes research. We need to know if patients in the U.S. are truly more likely to undergo regular screening with virtual colonoscopies than regular ones. I don't think we have that data yet.

Lastly, I think we need to know when is a professional society

or government agency going to address the health threat of increased lifelong exposure to radiation from medical tests and treatments? The advent of electronic medical records provides the opportunity to implement a plan to reduce patients' total exposure to radiation. That wouldn't cap it, but rather allow providers to make informed decisions by enabling them to review a patient's previous radiation exposure before choosing what kind of screening to recommend.

DR. TALAMINI: You're under 60 seconds.

MS. FRANCE DE BRAVO: For example, a heavy smoker undergoing a regular CT scan for her lungs should probably get colonoscopy screening rather than CTC since the latter also exposes part of the lungs to radiation. And I thought that was another interesting point Dr. Summers raised is the notion that these CTCs could possibly give us other important data for screening, whether it's on visceral fat or on bone density, thus increasing the benefits yielded and weighing that against the harm.

So we are concerned very much about lifelong radiation exposure from that. And we want to know does this really -- is this really more acceptable to patients so we can improve uptake of colorectal cancer screening. Thank you.

DR. TALAMINI: Thank you very much.

The next speaker is Dr. Richard A. Frank from the Medical Imaging and Technology Alliance.

DR. FRANK: Thank you. My name is Richard Frank. I'm the Chief Medical Officer at Siemens Healthcare, and I'm here to represent MITA, the Medical Imaging and Technology Alliance. MITA appreciates the opportunity to contribute to today's deliberations.

MITA is the leading trade association representing medical imaging, radiotherapy, and radiopharmaceutical manufacturers. MITA and its members develop quality standards for medical imaging equipment. And of particular relevance to today's meeting are our innovations for dose reduction.

CT colonography has come a long way in the last five years. Other speakers have presented the cumulative evidence for safety, efficacy, and economy in the use of colonography for early detection of cancer. This innovation is important because it addresses one of the main reasons for non-compliance with screening recommendations and therefore offers the prospect of better outcomes achieved more cost effectively by virtue of earlier detection in a larger segment of the at-risk population

In response to exhortations by the FDA and others, the CT community has developed a set of quality standards, and the innovator companies have implemented these in the design of their products, which now enables quality images at lower dose radiation. Participation in this standard setting initiative was broad, including notably the FDA and the International Atomic Energy Agency.

MITA member companies then developed these standards and incorporated them into the design of CT, fluoroscopy, and interventional radiology products. Today I'll speak only to the standards for CT. A number of standards were implemented as guidance in the design of these innovations. These standards, developed in conjunction with FDA and others, as just stated, provide guidance to MITA member companies in the design and manufacture of CT products.

Standard XR-29, otherwise known as the MITA Smart Dose, includes four components: a structured reporting of radiation dose; pediatric and adult reference protocols for image acquisition; automatic exposure control; and what we call dose check, which specifies an equipment feature which sets off an alarm, that is both notifications and alert messages, prior to scanning if the estimated dose of radiation would exceed preset levels.

There are seven innovations implemented in the past few years in response to the exhortations from FDA regarding radiation dose and in compliance with the standards just mentioned. I'll highlight just one of them by way of example. Iterative reconstruction is a software product for post-acquisition processing, which enables image quality at lower dose.

Innovations in CT detectors and post-acquisition processing has maintained image quality at lower dose. As a point of clarification, the dose necessary for CT colonography is inherently lower than the dose for standard CT of the abdomen because it's a different type of image acquisition

detecting the difference between tissue and air, somewhat analogous to low dose CT for lung cancer screening.

Now, this slide shows the radiation doses typical of colonography. At the time of the ACRIN, the national CT colonography study as Dr. Dachman explicated this morning, a typical dose was 7-8 mSv. Today the typical dose is about the same as that which each of us is exposed to from naturally occurring radiation sources in a year, or about 3 mSv. On the near horizon is a further reduction to 1 mSv, and, in fact, even today 2 mSv is being achieved at institutions with the most modern hardware and software.

Time did not allow detailed review of each of the standards and innovations, and we would welcome the opportunity to provide additional granularity on any of them, as this committee may require.

In summary, then, CT colonography has come a long way in the last five years. Other speakers have presented the cumulative evidence for safety, efficacy, and economy in the use of colonography for early detection of cancer. These innovations by technology companies working closely with FDA and other key stakeholders, including hospitals, are important because they address one of the main reasons for non-compliance with screening recommendations and offer the prospect of better outcomes achieved more cost effectively by virtue of earlier detection in a larger segment of the at-risk population. Thank you.

DR. TALAMINI: Thank you, Dr. Frank.

The next speaker is Dr. Douglas Rex from the American Society of Gastrointestinal Endoscopy.

Dr. Rex.

DR. REX: Hi, I'm Doug Rex from Indiana University. I'm a gastroenterologist, and my comments are on behalf of the ASGE and the ACG.

The ACG and the ASGE are participants in a multi-society task force and therefore endorsed CTC as a screening test in 2008. But the threshold for admitting tests into that guideline was very low. We've elaborated in other places our specific positions, which endorse colonoscopy as the best first test for most Americans. And we continue to endorse the 2009 CMS position to not cover CTC for screening.

There is a widely held misperception that increasing the number of screening tests will improve adherence. However, randomized controlled trials have shown that offering multiple options doesn't increase screening rates. And one of these tests specifically looked at CTC.

A recent randomized controlled trial of sequential testing in which the single best test is offered first and then refusers are offered other tests showed that this maximized adherence and also maximized the use of the most effective test. And we think that the dominance of colonoscopy in the United States using sequential testing and offering other tests when colonoscopy is refused will displace the fewest patients from polypectomy, which is key to cancer prevention.

There was a Dutch randomized trial laxative-free CTC that showed better uptake of CTC, but screening colonoscopy is hardly used there so the results really can't be extrapolated to the U.S. And two of the results could have influenced choices. First of all, the pre-procedure expectations compared to the post-procedure experience, it was much worse for CTC, whereas just the opposite was true for colonoscopy. And in the United States where efficacy is most important, colonoscopy outperformed CTC with 30% more advanced lesions detected.

It's widely stated that CTC has comparable effectiveness for detecting large lesions, but I just pointed out the recent Dutch randomized trial in which that wasn't the case. There's another randomized trial from the UK where there was comparable effectiveness, but 30% of CTC patients had to undergo colonoscopy. And just reported this month, the actual community experience in the UK national bowel screening problem in FIT positive patients was that twice as many patients with cancer were detected with colonoscopy and nearly twice as many patients with advanced lesions.

We've heard that there's poor sensitivity for lesions in the 6-9 mm range. This is a group of patients that we think U.S. patients want and deserve to have detected and removed.

We've also heard that there's really no direct evidence about serrated lesions, but there's some indirect evidence. Nearly 10 years ago, Pickhardt reported that there was reduced sensitivity for non-adenomas.

And Zalis recently reported that the per-patient sensitivity for adenomas 6 mm and larger was 59%, but that same measure for polyps of any histology was only 47%, suggesting that there was very poor sensitivity for sessile serrated lesions.

We're also quite concerned about poor specificity. When patients are referred for radiographic studies and lesions can't be found, it leads to longer and therefore riskier colonoscopies. And oftentimes when a lesion can't be found, patients are referred to a repeat of the radiographic study. In the ACRIN study, the specificity for lesions 10 mm and larger was 86%, the positive predictive value only 23%, and in the elderly we heard that the specificity was 83%. That would mean that 1 of every 6 Medicare patients undergoing CTC would undergo colonoscopy for a lesion that's not present. That's a specificity that's too poor.

So in the absence of evidence of improved adherence to screening in the U.S. general population, no evidence that CTC can achieve acceptable sensitivity for serrated lesions, continued inconsistent results even for large lesions but particularly for 6-9 mm lesions, problems with specificity, and then other ongoing controversies, we think that the current position, which is that colonoscopy dominates screening in the United States and when patients refuse colonoscopy other tests are utilized, remains the best one for American patients. Thank you.

DR. TALAMINI: Thank you, Dr. Rex.

The next speaker is Dr. Elizabeth McFarland from the Society of Computed Body Tomography & Magnetic Resonance.

DR. McFARLAND: Thank you very much for the opportunity to speak as a radiologist.

I'm going to just briefly hit some of the further validation trials. And as we look at screening cohorts, we've undergone the Navy trial and the ACRIN trial.

There are the -- excuse me. Can I just stop a second? These were the other slides. Could we go to the -- I'm sorry. I had made a change. I had actually -- if I could start my time -- included some of the non-screening trials and that's why I had made the slide changes, so forgive me. Under the revised, if we can have that?

DR. TALAMINI: If that may take a while we can --

DR. McFARLAND: Would there be another speaker or --

DR. TALAMINI: -- all our speakers?

DR. McFARLAND: I can show them -- the revised. Would there be one other speaker to speak while I --

DR. TALAMINI: Let's have Jasmine Greenamyer, if you're willing to speak? I think you're without slides, correct? And we'll just switch the order. So this will be Jasmine Greenamyer, Interim CEO, Colon Cancer Alliance, for 5 minutes.

MS. GREENAMYER: I'll gladly help Dr. McFarland.

Again, Jasmine Greenamyer with the Colon Cancer Alliance. I'm the Acting CEO. I'm up here to do more of the social science perspective giving the patient perspective on this issue.

I'm speaking on behalf of our board, our medical scientific advisory committee, and our patients. Our medical scientific advisory committee was in agreement in this, and they are GI surgeons, oncologists, what have you.

So to shortly go into this, our mission is to knock colon cancer out of the top three cancer killers. And as has been covered in different ways, awareness may be high that people can get screened for colon cancer, but screening rates are still too low. And public knowledge that this is one of the few cancers that is preventable also is sadly still too low. And there's a great amount of confusion in the community as far as what's a covered test versus what is not. And this would be a very apropos example of confusion in the patient community.

So as we've discussed in the more scientific end of things, that CT colonography has been shown to be an effective alternative. It is an attractive test to patients because of cost, recovery time, et cetera, particularly in military populations and some special subset populations. And patients often present with medical reasons where this is an attractive test. By and large, I do agree with Dr. Rex that colonoscopy is the predominant standard, the gold standard of sorts, but we also need an alternative test that

can detect pre-cancerous polyps. And, therefore, this is an attractive one to our patient community.

In sum, the Medicare population should have access to all effective screening methods. And the best test is the one that you do, and for a subset this is a very attractive option that we would like to see covered. Thank you.

DR. TALAMINI: Thank you very much.

Dr. McFarland, are the slides in order?

DR. McFARLAND: Yes, they are.

DR. TALAMINI: Thank you.

DR. McFARLAND: So I'm going talk about validation as well as patient preference. And we've heard about the DOD trial with the ACRIN trial, and I'm going to continue on with the Munich trial done in 2009, which was already presented. But to demonstrate how this exploited the new technology of -- compared to the DOD trial of 4-row to 8-row detector CT, it went on to 64-row detector CT. And I also -- it was asked before about a follow-up trial that was done at University of Wisconsin. The higher risk cohorts we won't cover, but those were in our submitted comments.

So the Munich trial had exploited the new technologies of 64-row CT and also done -- very much mimicked what the DOD trial had done, including segmental unblinding. We saw its good results in terms of both per polyp and per-patient sensitivity and specificity. One thing I'd like to say

about the serrated adenoma question is that when you look at all of the validation trials done to date in terms of screening cohorts, and of those false negative analyses that are always done within those tandem studies, there has not been a predominance of CTC misses based on serrated adenomas in the right colon. So I just -- because all of these tandem studies that have CTC with optical colonoscopy as its reference standard look at these false negatives. And there has not been a trend towards that. It certainly is an important lesion, and it's one that I think both technologies are becoming more aware of in how to detect it.

This is an important one though that we haven't talked about. And among the Wisconsin University, they did a five-year follow-up for over 1,000 patients who had a negative CT colonography under the paradigm of not reporting polyps 5 mm and less. They found in those patients 11 advanced adenomas, in general, 0.2 cancers per 1,000 patient years. And that is less than the incident cancer rate at optical colonoscopy of 1.7-2.4. Now, granted that is CT to CT, but it shows that in this very specialized program where they are using the paradigm of not calling the 5 mm and less polyps, that it continues to be feasible.

Patient preference. We know that there's still a burden in terms of eligible patients not adherent. And, obviously, all here know that it could lead to greater adherence to better understand patient preferences.

Now, I'm going to present three studies, and the last one I think

you'll be interested in. These first two you've already been exposed to in terms of patients who already are compliant and have gone through CT colonography. This is the CHI study. And when asked in terms of expectations before why did you choose CTC? Convenience, recommendations by the PCP, and safety. If it was not offered, would you have undergone colorectal screening? And, again, 37% said no, if they did not have CTC. And then, after completion of the CTC with a prior OC that had been done -- optical colonoscopy had been done at the time period before that, 95% have preferred CTC.

Now, we have looked at -- you've seen this slide before in terms of how we -- several of these studies have shown increased preference. And although the economics are not yet described to these patients -- we can't describe those ourselves because the screening is limited in terms of reimbursement. But I think what these studies do reflect are the following: that the patients get through it without sedation -- that's part of the positive -- without the pain, and they don't have the issues with the driver or the time away from work.

So in terms of that caveat of issues, I think that's what drives the preference studies from what you've seen. Granted, they need to be qualified for some of the concerns that have been listed.

DR. TALAMINI: About 60 seconds.

DR. McFARLAND: This is the last study though and this -- I'm

going to pass over this one. This is the study you already saw from Wisconsin.

This is now preferences among racially diverse patients in 212 patients within Michigan and Baylor, and this was across whites, African-Americans, and Hispanics. And they came up with eight hypothetical scenarios across five attributes. That is, what does the test involve as in collecting stool or a scope with or without sedation; prep needed; accuracy for finding cancer; discomfort or test frequency. And then the sixth test included those that were established from optical colonoscopy to barium enema and the new test.

And in order of importance of the attributes, we can see that 37% of all patients cared about what the test really involved compared to the accuracy and the test frequency. Again, this is among all patients, and they did show racial differences that I can't go into. But the results of the preferred test, again among the four established tests, they preferred in these hypothetical scenarios 37% optical colonoscopy, the most compared to flex sig. But among all tests, the new tests of virtual colonoscopy and FIT actually were higher.

So, again, we need to tailor our patient preferences to improve adherence, but it showed that in terms of that kind of scenario, that there was an interest in terms of the novelty of virtual colonoscopy. Thank you.

DR. TALAMINI: Thank you, Dr. McFarland.

The speaker is Dr. Shuai Leng from the American Association of

Physicists in Medicine.

DR. LENG: Thank you. My name is Shuai Leng, and I'm a medical physicist at Mayo Clinic in Rochester, Minnesota. I'm here representing the American Association of Physicists in Medicine.

A medical physicist is trained in, among other things, the use of -- radiation to diagnose and treat human illness. My goal today is to present the data of radiation dose from CTC. And this presentation was prepared jointly with my colleague Dr. Cynthia McCollough, also at the Mayo Clinic.

When we talk about radiation dose, we have to differentiate the radiation dose generated by the scanner and the radiation dose that's absorbed by the patient. The scanner report radiation dose using a internationally standardized metric called volume CT dose index, or CTDIvol, which is available to the operator and also recorded in dose information page, as shown in the figure. However, CTDIvol is not patient dose. To calculate patient dose, we have to take into account the patient size and the attenuation.

In the year 2011, AAPM Report 204 introduced a concept called size-specific dose estimates, which take into account both the scanner output and the patient size. And this has been quickly adopted by imaging community. If we look at the CTC dose, American College of Radiology practice guideline stated that a total CTDIvol for both the supine and prone scan series should not exceed 12 mGy. And this corresponds to SSDE roughly

12.5 mGy for --

The ACR Dose Index Registry collects CTDIvol and other specific information from patients submitted at over 800 facilities. And in a sample of 3500 patient, the CTDIvol, the medium CTDIvol was found to be 9.7 mGy. The SSDE is a relatively new concept, so it has fewer patient, but over 50 patients the medium SSDE was found to be 9.6 mGy. So from both the practice guideline and from initial survey of actual patient data, we found SSDE of the CTC is about 10 mGy. And this translate into effective dose similar to the annual background radiation. And with advancing technology, this dose is going down further.

In May 2012, the United Nations Scientific Committee on the Effect of Atomic Radiation stated that increases in the incidence of health effects in populations cannot be attributed reliably to exposure to radiation at the levels similar to the background radiation.

This data from atomic bomb survivor lifespan study, and it demonstrated a linear relationship between the number of excess cancer incidence to the radiation dose to the colon, if we look at whole spectrum of the radiation dose. However, the CT dose is here, and if we spanning the scale to look at data more probably relevant to today's discussion, we found out that between 1 mGy to 100 mGy of colon dose, there are no increased incidence of cancer.

And as we mentioned before, from the ACR Dose Index

Registry, the CTC dose medium range is about 10 mGy, well below the 100 mGy where we started to see the increase to cancer risk. Actually, if we're using a model, a lot lower dose threshold, the threshold is about 40-85 mGy. However, this was not significantly better than the linear no-threshold model. Therefore, LNT is still used due to its simplicity. But we have to realize that LNT cannot represent the observed lack of increased cancer risk at the low dose range, which CTC follows.

That's why AAPM and the Health Physics Society published their official position statements. It basically says at effective dose below 50-100 mSv, the risk of -- radiation are either too low to be detected or do not exist. And the predictions of hypothetical cancer incidence and death in patient population exposed to such low doses are highly speculative, and it should be discouraged because this can cause harm to our patients as they lead to sensationalistic articles in the public media, and it cause patient to refuse medical imaging procedures that they can benefit from.

So, in summary, at a low dose of CTC, and affecting almost all the diagnostic imaging examinations, long-term health risks are either too small to be conclusively demonstrated or do not exist. And it's the position of AAPM that in the context of a low dose examination in a population of older adults, radiation dose is not a safety concern because of CTC for the screening of asymptomatic patients for colorectal cancer.

Thank you for the opportunity to present data.

DR. TALAMINI: Thank you, Dr. Leng.

Our next speaker is Dr. David H. Kim from the Society of Abdominal Radiology.

Dr. Kim.

DR. KIM: Thank you. I'm from the University of Wisconsin and will be speaking on behalf of the Society of Abdominal Radiology.

The Society of Abdominal Radiology and its 700 specialized radiologists strongly support the use of CTC in the evaluation of colorectal pathology. As abdominal imagers, we use CTC daily in clinical practice, and we see how effective this test can be. And this is why CTC is steadily replacing barium enema.

I want to draw your attention specifically to the issue of incidental extracolonic findings. This has been raised as a concern as a potential detriment to CTC leading to increased cost, patient anxiety, and complications. But, fortunately, we have a fair amount of data about this.

So extracolonic findings are possible due to the cross-sectional nature of CTC. And it's supposed to be -- however, it really is a balance between benefits and burden. So on one side we have -- we're going to increase the number of workups for findings, many of which are benign, but we are going to be making important diagnoses here, including extracolonic cancers and abdominal aortic aneurysms.

So, again, you can see there's a wide or a large amount of data

here. And let's start first on the burden or cost side. The prevalence has been reported at 60-70%, but it's important to realize that doesn't mean that 70% of CTC exams are going to generate an additional exam. Many of these are not diagnostic dilemmas or cause additional imaging. Here we have a small renal calculus in the right kidney. We don't do additional exams. This just helps -- when the person comes to the ER with flank pain, we know what exactly is going on.

So a better measure is that of looking at those findings with potential clinical significance that we request an additional evaluation. And when you do that, the range drops to 7.4-16%.

But perhaps the best measure is to look at the actual workup rate, do a careful medical audit of that group of cases where we say we need additional imaging. And when you look at series after series, this number decreases down into the 6-8% range. This translates to an increased cost to CTC about $24 to $34.

Now, there are series that show numbers that our frame shifted significantly upwards. I would urge you to look critically at these study populations because these are symptomatic high-risk populations. The colorectal cancer prevalence of these groups are 10-14%. These are not average risk healthy adults. When you look at that group, the number is closer to 6-8%. And this is definitely reasonable when you look at the benefits that happen with extracolonic findings.

And what are they? Well, clinically significant diagnoses in 2.5%, extracolonic cancers were seen 3-6 per 1,000, abdominal aortic aneurysms 4-8 per 1,000. And if we were to look at asymptomatic populations, the numbers further increase to 1.1% for extracolonic cancers and to 2.1% for aneurysms. At UW we've screened about 10,000 patients, and what that translates is to 1 extracolonic cancer for every 250 screening patients, and 1 aneurysm for every 200 screening patients. And these are completely unsuspected. I think it's important to realize that these are just not numbers. These are people.

So here's a 60-year-old Wisconsin native, pretty stoic guy, really didn't want to undergo cancer screening because he feared the colonoscopy, had a large caring family, they really pushed him hard, and finally he got screened by CT colonography. Nothing in the colon, no cancer, no advanced neoplasia, but what we saw -- and here with contrast you can see a 6.7 cm aortic aneurysm. There's a nice horseshoe kidney draped over the top. And so, this person underwent aortic stent repair and now is five years out and doing well. So this is a huge save. There's a good chance this stoic person would have not presented until symptomatic rupture.

So, to conclude, again, the Society of Abdominal Radiology strongly supports the use of CT colonography. Specifically, the issue of extracolonic findings, the evidence shows that the benefits clearly justify the burden or cost. Furthermore -- and we'd be happy to give you more

information on this -- we believe that CT colonography is effective, has an excellent safety profile, and when instituted in a particular region increases screening adherence. Thank you.

DR. TALAMINI: Thank you, Dr. Kim.

The next speaker is Kim Ryan, Director of Patient Information Services from Fight Colorectal Cancer.

MS. RYAN: My thanks to the Panel for allowing me a few minutes today. I think I'm probably your last commenter. And I think that's probably because I signed up last, so I'm happy to be here.

These comments are submitted on behalf of Fight Colorectal Cancer, a non-profit, non-partisan advocacy organization that is committed to the fight against both colon and rectal cancer.

Fight Colorectal Cancer is a leading colorectal cancer advocacy in Washington, D.C., empowering survivors to raise their voices against the status quo, training advocates around the country and educating lawmakers and pushing for them to make better policies. We offer support for patients, for family members, and for caregivers, and we serve as a resource for colorectal cancer advocates, policy makers, medical professionals, and healthcare providers.

Additionally, we do everything we can to both increase and improve research at all stages of development for all stages of cancer. Fight Colorectal Cancer firmly believes in disclosing all potential conflicts of

interest. We have worked with many companies who have an interest in novel screening methods for colorectal cancer, including Exact Sciences, Given Imaging, and Epigenomics. None of these companies nor our other corporate sponsors have influenced our comments on this issue.

So you've already heard many of the risks and benefits of CT colonography today, so I won't belabor those points. However, as you discuss the issue of CT colonography today, we would like you to take a step back and look at the larger issue. And that is access to colorectal cancer screening.

A critical barrier to colorectal cancer screening in the past has been lack of insurance. A study from the CDC in 2008 found that in the insured community, screening from 55% in 2002 to 66% in 2008. However, in the uninsured community, that screening rate in 2002 was only at 33% and only increased to 37% in 2008.

As was mentioned before here today, the advent of the Affordable Care Act has the potential to greatly increase screening as it requires that all private health plans cover colorectal cancer screening test with the U.S. Preventive Services Task Force rating of A or B without any out-of-pocket cost to patients.

Importantly, the recommendations say that the level of evidence for CT colonography and stool DNA testing is insufficiently defined as the USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor

quality, or conflicting and that the balance of benefits and harms cannot yet be determined.

While many novel screening tests are either on their way to market or quickly approaching the FDA for approval, insurance companies are unlikely to cover them without a change to the USPSTF guidelines. We realize that the USPSTF guidelines will change only in the face of significant and compelling data, which is as it should be. At the same time, the companies involved with these new screening tests, especially smaller device companies, are unlikely to either have the capacity or the desire to conduct a large, long, and costly population-based trial to generate the required data.

Where the public would be best served would be by breaking down the silos between CMS, the FDA, and the USPSTF. The FDA has the ability to approve devices which they deem safe and effective, and CMS has the ability to reimburse for novel screenings under the coverage with evidence development mechanism. Combining FDA approval with some form of CED status could result in a registry that would provide critical answers to critical questions, a lot have been asked here today.

Do the novel tests increase screening in patients reluctant to undergo colonoscopy? Do the novel tests increase access to services in both rural and underserved communities? And do the novel tests result in decreases in death due to colorectal cancer?

Screening saves lives by finding and removing pre-cancerous

polyps and by detecting cancer when it's early and then curable. However, 1 in 3 Americans who should be screened are not being screened, even though a recent article identified colorectal cancer and cervical cancer screenings are two of the most impactful cancer screenings.

Therefore, we urge you to strongly recommend that the FDA use its convening power to engage with CMS, the USPSTF, and other appropriate stakeholders to look for a way to generate the data that would help both the public and providers make better informed decisions. We are ready -- Fight Colorectal Cancer is ready and willing to engage with you on this issue, if and when we might be asked.

Thanks for the time to comment.

DR. TALAMINI: Thank you very much.

Does anyone else with to address the Panel at this time? If so, please come forward to the podium and state your name, affiliation, and indicate your financial interest.

(No response.)

DR. TALAMINI: Okay. Seeing none, I'll ask the Panel, do any Panel members have questions for any of the Open Public Hearing speakers?

Dr. Dauer.

DR. DAUER: Yeah, this is for Dr. Rex from the ASGE. We will need a brief reply, by the way, Dr. Rex.

DR. REX: Okay.

DR. DAUER: In your presentation you said that there -- when patients were given multiple options, there was no increase in the percent that were undergoing screening when they were offered the options. And you used that to substantiate that by three articles, but they were sort of out of date. They were 2004, 2005, and 2006. So the newest article you had was over seven years old. Is there anything in more current data that would tend to prove that or justify that position?

DR. REX: Well, they're the only randomized controlled trials that are available. And randomized controlled trials I think are the most powerful forms of evidence. So we hear a lot about preferences in patients that are undergoing procedures, but the bottom line is whether a given test can actually improve adherence rates. And so, from the three most powerful studies that we have, they suggest that offering multiple options doesn't do that.

And as I said, this recent randomized controlled trial from 2013, which compares sequential testing, showed that it maximized adherence and got the most effective test done. If you get the most effective test done the most, you'll get the most polyps removed. And it's polypectomy that actually leads to the prevention of cancer and nothing else. It's polypectomy that does it.

DR. TALAMINI: Thank you, Dr. Rex.

Any other Panel members have questions for the public

speakers?

(No response.)

DR. TALAMINI: Seeing none, we will go ahead and take a 15-minute break. It is currently 2:40, so we will reconvene at 2:55 sharp, at which time we will begin the Panel's deliberations.

So, again, don't discuss any of the issues during the break, but think about what your summary might be for these issues. Thank you.

(Off the record.)

(On the record.)

DR. TALAMINI: All right. I'd like to call the Panel back to order. It's now 2:55.

We'll now proceed with the Joint Panel discussion. Please show the slide with the questions for discussion. These questions also are in your packets. Panelists, please remember to speak into the microphones.

And for this portion particularly, it's a little awkward, but we need you to identify yourselves before you speak because we have such a large number here. Otherwise, the transcribers will have difficulty knowing who is speaking. So mic on, state your name, say what you got to say, and microphone off.

By way of comments, we have a total of three hours. If every Panel member speaks for eight minutes, that's the three hours. So we want to make sure we engender the discussion and the interaction as much as

possible, and to get the points out that these experts around the table have.

So with that being said, I think the way we will do this is to read Question 1a and ask for discussion around that, and then Question 1b, and then Question 2.

Considering available colorectal cancer screening tools and current colorectal cancer screening recommendations, please discuss the currently available data and information on:

a. The potential benefits of CT colonography for the screening of asymptomatic patients for colorectal cancer, including test performance characteristics, impact upon overall numbers of patients screened, and extracolonic findings.

And I think rather than the normal protocol of going around the table, I'll just ask those who have formulated their thoughts on that Question 1a to go ahead and volunteer and speak. Don't be surprised, however, though if I call on some individuals who have been very quiet so far to draw your opinions out.

So with that said, Dr. Dauer.

DR. DAUER: All right. Thank you for the opportunity to present my comments here. I first want thank the opportunity to be here today. I've learned a lot about this, and I did come in with an open mind on this.

But I think one of the important points about 1a to consider is that from what I've seen today, there is increased patient acceptance. I think

patients are more likely to undergo screening with CTC, although the problem is the smaller lesions 6-9 and under 6 are not as readily detectable. Those also have more time to be detected at the next time.

I think in the ACRIN series, we saw that there was a 90% sensitivity for lesions of 1 cm and above, which is our important finding. And the perforation rate and complications were very low. So all in all, I would say that with the evidence that was seen here today, there seems to be increased patient acceptance, very good sensitivity and selectivity.

And the one thing I haven't heard anybody talk to about today is with the advent of screening with the Affordable Care Act, although we don't know exactly what form that screening is going to take, I don't believe -- and maybe you can help me on the GI side -- if there is enough colonoscopy time available in the country to start screening all these patients just with OC. I don't think there's enough capacity as far as number of doctors or facilities if we didn't use CTC for screening because of the increased volume of screening in patients that we'll be having. Thank you.

DR. TALAMINI: Thank you, Dr. Dauer.

Dr. Ahlgren.

DR AHLGREN: Okay. I'll follow your instructions to identify myself, James Ahlgren, medical oncologist, Professor of Medicine and Pharmacology at George Washington University.

And I'll limit myself to the benefits, subtitle a. We'll go to the

safety issues I guess on a second time around.

I think we've heard enough -- and in my reading -- to form the conclusion that CTC has sensitivity at least down to about 8 mm comparable to optical colonoscopy. And the ability of CTC to detect these lesions, I don't think there's really any question about it at this point in time. And the selectivity is certainly quite adequate.

It's quite a bit trickier to answer the question of whether and how much of an impact this will have on adherence to screening guidelines. We know that about one-third of patients in the United States are not screened according to guidelines. We know that the acceptability of what has up to now been regarded as the gold standard of optical colonoscopy is approaching 50%.

I don't think that we can expect the availability of yet another study, regardless of how much benefit it has, will pick up all of the patients who are not being screened. There are many reasons those patients are not being screened. And the fact that they would prefer some other test is not probably the biggest one. Many of these patients have never been offered colonoscopy.

As a medical oncologist, I'm often referred patients from the emergency room or elsewhere, and I find that one of my early duties is to find this patient a doctor because they have no primary physician. Nobody has ever suggested to them to have colonoscopy. So we're not going to pick up

that difference between 50% and 100% or even between 70% and 100%. It'll be less than that. But even if there are any patients who will choose CTC and would not otherwise have adequate screening, then we should offer this to them. I think that there's enough evidence that the benefit is there.

As far as the extracolonic findings are concerned, I think that's a benefit. I think the medical community will take advantage of it in patients who have them found, but I don't think we should consider that in making this decision. This decision is really based upon is this an appropriate test for screening the asymptomatic population. And I think it is.

DR. TALAMINI: Thank you. And, again, I would remind the Panel we're not driving towards an up or down vote here. The value is in the discussion and in your views.

Ms. George.

MS. GEORGE: This is Elisabeth George. I'm here as the Industry Rep, so I'm the very non-clinical one here. So I'm going to give you a couple of perspectives that I have.

I think what I heard in all of the data -- and I actually read all those documents that they sent us, so it helped me sleep this weekend. But it did seem there was an equivalence in the choices. And I think one of the things that people do like is having a choice. And I think as -- I'm in that age bracket. One of the things that a lot of people like is a technical choice. They don't want to have the old fashioned way that something's been done, so I

think that that's something that should be considered.

I think that the speed at which the patient can be processed -- we all have very little time to do things, so the faster a patient can get in and out and have an effective solution. And I think that there is a lot of data out there. And from the sounds of some of our presenters at the public meeting, there's a lot more data that we didn't even get to look at. There's a lot of registries that are collecting information that I think probably are already showing that there's value in this. Thank you.

DR. TALAMINI: Thank you.

So in the interest of generating the discussion, the consensus so far that's emerging is equivalence and that the sense that this should be expanded and perhaps could improve screening rates.

I want to ask the Panel if there is somebody who either strongly or even mildly has the opposing point of view that would want to bring that forward at this time? That's not to say we're done discussing it. I just want to make sure we have the expansion.

Dr. Fogel.

DR. FOGEL: First of all, let me start by saying that I think that there is going to be a role for screening colonoscopy, but there are a number of concerns that I have. And my comments are basically the pros and the cons -- or the pros and then the concerns. And the concerns are based in part upon the lack of data.

I think that based on the material that we read and we heard this morning, the sensitivity, specificity, predicted value of CT colonography in the hands of the experts and the researchers who did the studies today shows that it is equivalent to optical colonoscopy. I think that there's no doubt that there's a low level of discomfort with a CT colonography. And I think that there probably would be an increase in the numbers undergoing screening for colorectal cancer if CT colonography became an available technique, but I have a number of concerns, and they're as follows.

I think that we've minimized the effect of training and experience in how that is necessary to perform an adequate study. In one of the Wisconsin papers that was published within the last year, they found that there's variability in the performance of their eight radiologists who were reading CT colonography. And when they recalculated their data, excluding one of their eight who had done at least 130 procedures, they found that their sensitivity and specificity went up. So if the people who are -- if there's variability in performance among those who are expert, what can we expect from those who are going to be learning the procedure and not having the expertise and not having the access to the thought leaders that have really promoted the technique?

My second concern is one of adherence. We know that people will show up for their first screening CTC. There's been no data that was presented that showed that people will show up for serial CT colonographies.

And since screening for colonoscopy is a procedure that will -- screening for colorectal cancer is a procedure that lasts -- it requires 25 years of screening, we don't actually know that there -- what the long-term benefits of CT colonography is.

The question of flat lesions and serrated adenomas I don't think has been adequately addressed.

And my last concern is related to what actually happens should this technique become available in the community. The decision as to where to send a patient will be determined by primary care doctors. Now, it's really going to be open access for CT colonography. The patients are going to be referred by their primary care doctor, and I don't think that you're going to find that same homogenous population that we see in the studies. You're going to have people that have abdominal pain, you're going to have people with guiaic positive stool, and it's not clear necessarily that the results will be as good as what we saw in these tightly controlled studies.

And there's a concern that in this day of limited resources, that we're going to have wasting of resources because patients are not sent for the appropriate test. I think that if CT colonography becomes a technique that is approved and becomes accepted, we need to have clinical decision tools to help physicians manage their patients and send them for the appropriate screening test.

DR. TALAMINI: Thank you.

So, again, crisp and focused as you can be in the interest of time.

Dr. Charabaty?

DR. CHARABATY? I have to agree with many points that my colleague pointed out. I think most of us see that for polyps more than 10 mm, it seems that CTC is as good as optical colonoscopy, even though Dr. Rex presented some data that didn't show that.

But my concern is how it's going to be applied in the community. Here we're dealing with expert radiologists that use CTC. The patient gets shipped down to the endoscopy the same day. I just find it very difficult to see this being adopted in practice. And my concern is that losing a patient that had a positive CTC and has to come back another day and go through the prep again to get the polyp removed.

The second thing is for CTC and the question about polyps between 6 and 9 mm where the sensitivity is less and where we feel, well, they're not important at that time. But my concern is that is this going to give a false sense of security to patients that my CTC was kind of fine. And we all have patients that had no colonoscopy polyps and we tell them come back in five years, and they show up 10 years later. So -- even for those patients that they know that they had a polyp and an adenoma that was removed.

So my concern is that for a patient who had a CTC that was relatively normal that they might not come back for that next CTC at five

years, as recommended, and that we might be missing opportunity to prevent colon cancer that way.

The third thing is really the flat polyp. The images that were shown here really have nothing to do with the serrated polyp that we see on the right side of colon. They are very subtle. They're really not raised. We use sometimes a different technique of chromoendoscopy or virtual chromoendoscopy to pick up these serrated polyps, and they're usually larger than what was shown today. So I think for that issue -- and us as gastroenterologists, we're still striving for better detection for that with better preps and longer screening time and taking our time in the right colon. I don't think this issue has been addressed properly. And to say that they're not that important, well, we do know that 30% of colon cancer comes from these serrated polyps.

The other thing is I don't think we should confuse what patients prefer to the fact that they're going to be adherent to the recommendations because we do have a test and that's the FIT test. There's no prep. You can do it at home. There's no sedation. You don't miss anything at work. And we've heard from everybody that the compliance is a big issue and that people are not willing to do this once a year. So the fact that we ask patients that are coming for a screening -- so we're already selecting people that are interested in getting screening -- which one do you prefer?

And these studies were done by radiologists and not

gastroenterologists, so the way things are presented might be a little bit different, although I can't make really any comment on that. I don't know the details. It's something that we should interpret cautiously. It's not because the patients prefer one thing that they're going to be adherent to it.

And Dr. Pignone showed a very nice map of the United States where it seems that the same places are being screened independent of what type of test is offered. And Dr. Barlow talked about how despite CTC being available in his unit, in his radiology unit, it's underused despite effort of going to primary care and other physicians to send their patients for CTC. So I don't think preference really means that we're going to capture more people getting colon cancer screening.

It's definitely safer in terms of perforation. I have a question mark regarding exposure to radiation. I think we've heard that overall it seems that it's not a high risk, although 60 cancer related -- radiation-related cancers out of 100,000 seems a fair number after one CTC, and we know that patients are getting CT scanned left and right. I see young people mostly in my practice, and most of them at age 20 already received a CT scan for abdominal pain, for not feeling good, for fever, for diarrhea, et cetera.

So I think we do have to take into account not just the exposure during the CT colonography, but that patients have been exposed to other radiation from CT for other reasons, and we're just adding another test for that. But, overall, it seems like it's relatively safe in terms of this radiation.

Thank you.

DR. TALAMINI: Thank you.

Dr. Fennal?

DR. FENNAL: Mildred Fennal, Consumer Rep. I'm just going to come from a different perspective. The research that we've seen here, it gives us the potential benefit of using CTC. I think that it's great, but I think that it will happen only in certain geographical areas. It does not appear that it's going to be something that's going to trickle down to the less populous areas or to the underserved areas. And as the doctors have to send their patients someplace else, then we are providing additional expense and difficulty for those patients that have to go to these different areas.

As far as increasing the numbers of screening, that too will depend -- because the lack of patient participation in screening is a different issue. It's not that they don't know that that should be done that way. The patient -- I would like to really see those questions where the patient agreed that they wanted this test rather than the other. I'm the person that goes in the room after you all go in and explain the test that the patient's going to have, and most of the time they don't have any idea what you said.

(Laughter.)

DR. FENNAL: So I want to know -- and I would like to see those questions where it says I want this rather than that because most of them do not even understand what those tests are. So that's a question in my mind.

And as far as the discovery of certain extracolonic findings, I think that it's -- in some cases it will be beneficial to the patient because it may save a life. But depending on the age, the health status of the patient, it may become a burden to that patient and family, so I'm not sure about where that comes from.

DR. TALAMINI: Thanks.

So, so far we've heard the sense that there seems to be equivalence from the data in large part, and we've heard some express their concerns about this. And what I would say at this stage is if you agree largely with one or the other and don't have a lot to add, stating that would be helpful in the interest of time and in the interest of knowing where the balance is here.

On the other hand, if there are issues that have not yet been brought out -- we haven't heard about the Medicare issue very much, we haven't heard about a few of the other things that had been brought up -- again, focusing on (a), not (b) quite yet, that's what we need to hear in this part of the discussion going forward.

Dr. Coldwell.

DR. COLDWELL: Hello. Doug Coldwell, University of Louisville.

I believe that CTC has a role. It's just another option. I think giving people options is a good thing. It certainly will give people fewer excuses not to get screened.

But I think that there are two aspects of this that have not been mentioned. One is -- Dr. Fogel alluded to it -- the training issue for the radiologists reading the CTCs should be rigorously promoted. Secondly, and as important with this is that this is a joint effort between the radiologist and the gastroenterologist. We are not at war with each other. We are here to serve the patient and serve the patient's best interest.

So I think that centers of excellence are going to develop where the communication between the radiologist and the gastroenterologist is a natural thing. And that I sincerely believe that in order to get the maximum benefit from CTC and optical colonoscopy, that this is going to have to be both of us moving forward -- well, I was going to say hand in hand, but -- thank you.

DR. TALAMINI: Thank you.

Dr. Foxx-Orenstein?

DR. FOXX-ORENSTEIN: Thank you. If CTC were a therapeutic as well as a diagnostic tool, I would say we wouldn't even need to have this discussion. However, colonoscopy is by and far the best diagnostic and therapeutic tool. And my fear is that CT colonography, if it becomes as accepted as a screening tool, that the recent association with colon cancer incidence rates decreasing will actually level off and perhaps go up. Because what we don't find at an early stage will be diagnosed at a later time as a cancer.

DR. TALAMINI: Thank you.

Dr. Nostrant.

DR. NOSTRANT: I agree -- Tim Nostrant, University of Michigan. I agree completely with everyone's statements. The only concern I have is I think that CT colonography is going to be great for large lesions. We don't know the behavior of small lesions.

Remember that missed colon cancer with colonoscopy has been defined fairly well. There's been three reasons: number one, inadequately trained endoscopists; number two, flat lesions, which is the most common cause for right-sided cancer miss -- and I can tell you, having done now close to 100,000 colonoscopies in my career, I could tell you that that's the lesion I think I've missed two times because I just didn't see it. And I'm looking at it directly. I mean we have to do magnification endoscopy and chromoendoscopy to be able to see it, and even then we're not sure. The lesions presented today are much smaller, and clearly not the lesions that we talked about, which are sessile adenomas. Remember pathology has changed dramatically in these years in terms of describing this cancer.

And I think the second is -- and we've seen this with non-trained endoscopists. Remember the vast majority of colonoscopies in this country are not done by gastroenterologists. They're done by family practice docs. And there's a lot of them being done. They can't reach the cecum, and we're going to have the same problem in the community with radiologists

because it's not going to be the major focus of their practice. They're going to be a very small focus of their practice probably because of all the other things they have to do. That's not true for most colonoscopists.

DR. TALAMINI: So, Dr. Nostrant, let me just push you little bit, having done 100,000 colonoscopies. Having heard the data, read the data, do you think the flat polyp issue in the right colon -- I don't want to use the word invalidates -- but weakens the argument that CT colonography should be expanded?

DR. NOSTRANT: I don't know because Dr. Pickhardt presented -- I don't know because I think Dr. Pickhardt presented, or at least thought he had presented, data that showed that he saw many more lesions than what they reported. But since they're using size on CT for a visually not appropriate -- or for a visually not as discriminative thing as colonoscopy and magnification, I think what you're going to find is it's going to be missed. And that's really my major concern with this whole process is that that lesion is the number one missed lesion. I mean the rest of these -- I mean in the left colon and the transverse colon, we miss very little, but in the right colon we miss a lot. And I think that's the reason why.

DR. TALAMINI: Thank you.

Dr. Shiels.

DR. SHIELS: Bill Shiels from Columbus, Ohio.

As far as a benefit for a screening test and the potential to

increase access, I don't think there's any question that if patients have a second choice, no matter what geographic locality they live in, or what military base we operate in, if we have access to something that may be a little more palatable, we might just get access to care and prevent death, if we can.

As far as adherence and return to the CTC for a second round, speaking from personal experience, having had my first colonoscopy with conscious sedation, remembering every single plunge of the colonoscope into my colonic flexures, and wondering what was the sedation -- it was way conscious sedation -- it had nothing to do with sedation at all -- I remember it vividly. And I have plenty of people who will not return for a second colonoscopy. And whether it was the training or lack of training, I don't think there's an issue between the two technologies which patients are more likely to adhere to their screening and return for a second round of screening recommendations.

Training -- Dr. Nostrant, I appreciate the comments you made. The trained and untrained surgeons, gastroenterologists, family practice doctors, anybody that get their hands on a colonoscope is going to do the job, and it's a matter of chairmen and credentials committees enforcing accountability. It's what we did when we wrote the MQSA with the FDA. Accountability was a key part of us writing the MQSA, and I think it's a key part of educating the public. As a nurse educator, I think you would agree.

Education, no matter what technologies are available for access, if we can educate our patients to search out the best doctors, look at their credentials, question them before you let them put a colonoscope or a CT scan in front of them, to be accountable on both sides of the equation.

As far as extracolonic findings, we haven't' really touched on that much, but if the Postal Service lost 2.5% of all of the mail, they'd be out of business. If FedEx lost 2.5% of all of your packages, they would be out business. If we can find 2.5% of preventable deaths, we've made a major inroad. It's not an inconsequential point to be made as far as an option to give patients to have access to tailor their treatment and their screening to their own personal preferences.

And, lastly, those who can't undergo colonoscopy would have access to a test that could detect colorectal cancer, if they're unable to undergo colonoscopy.

DR. TALAMINI: Thank you.

So we're starting to look for strongly different points of view or aspects that have not yet been brought up.

Dr. Zhou.

DR. ZHOU: So I have say this on record. I have some doubt about validity of estimated sensitivity and specificity, ROC curve of both CTV, CTC, and OT because of the problem with the imperfect gold standard and also the reference standard is dependent of the test under study. We know

in the statistical literature, those are no go. There definitely is major flaw in the design. They do have some methods out there actually available for us to study how sensitive your estimator are based on imperfect gold standard.

I'd like to see more study and more analysis and to see whether we can trust those estimates in sensitivity and specificity, ROC curves, so I want to say on the record on that.

DR. TALAMINI: Thank you.

Ms. Aldrich, you've been quiet. You don't need to speak if you don't want to, but as a Patient Representative we want to hear your views, if you have them.

MS. ALDRICH: Sure. One of the things I find that's really important is understanding the culture in the communities that we serve and not assume that the patients have that in mind that they're coming to see the doctor. They're looking for the doctor to give them the answers. So in the communities that I serve, most of the patients don't come in with knowing what the options are, and they do tend to defer to the doctor to see what's going to be done, and the dictation comes from the doctor to the patient.

However, I do agree with the CDC that we should go forth with using and giving options to the patients so that they may at least have more options and more things available. And I do believe with that, the growing pains and everything that goes along with anything that's new to the market, or fairly new, eventually we will be able to work out the kinks and it can be an

effective tool.

DR. TALAMINI: Thank you.

Dr. Imrey.

DR. IMREY: Thank you. I'm largely in agreement with the thrust of the discussion thus far. I'd like to speak to two points.

One point is simply that this -- the issue of possible lost efficacy from CT colonography relative to colonoscopy seems to me to be largely conjectural. We do not have data that indicate the contribution of smaller than 1 cm polyps to reductions in colon cancer that may be occurring subsequent to the increased use of colonoscopy. And I just haven't heard any data, or read any data -- and I read the briefing materials -- with regard to that. So it seems to me that any program of colonography that's introduced should have an aspect that follows these polyps and tries to learn more about that.

In addition, it seems to me that the operating characteristics of a colonography program that's introduced -- that anyone that's introduced is going to be enormously dependent for both safety and efficacy profiles on the referral pattern to optical colonoscopy implemented by that program, both with respect to polyps and with respect to extracolonic findings.

And so, it might be advisable to accompany this -- in addition to aspects that encourage training of practitioners -- with some attempt to standardize the national referral protocols and in terms of the size of the

polyp or other characteristics that can be seen on colonography, and also with respect to extracolonic findings so that there's at least -- at least there are guidelines out there that show people how this technology can be offered with a pretty good apparent safety and efficacy profile.

I'd also like to comment in association with Dr. Zhou that there are lots of uncertainties about the data in this area, and they'll come up again with regard to safety. But it seems to me that we are making judgments -- we have to make judgments about -- it's better to make judgments on what we do know rather than to make judgments that are totally subjective.

And so, I think it's very reasonable to proceed even though the data are relatively uncertain because colonoscopy itself -- although it's become established and there I think is increasing evidence that it's very helpful -- is not really a gold standard, it's not set in stone, and we don't know precisely the degree and at what levels and how much -- and how it's helping us yet.

DR. TALAMINI: So, Dr. Applegate, we have you next, but the issue of the Medicare population, if there's a Panel member that wants to opine specifically on that, we haven't talked much about that.

Dr. Applegate?

DR. APPLEGATE: Well, I do want to talk a little bit about screening compliance. And so, I didn't want talk about the Medicare population per se, but I do want to talk about the HEDIS scores because a

couple people have said that there's not any evidence the CTC would necessarily increase compliance. And I am of the belief that there's benefit in CTC, so I'm not going to go through what other people have said.

And I'm a pediatric radiologist, so I don't do CTC. I have no intention of ever really seeing its use in children, but I do see that if we go back to Dr. Barlow's slide that he presented earlier, looking at the NNMC HEDIS data and the NNMC HEDIS data plus CTC, you will see that there is a pretty side discrepancy in cancer screening compliance, and that is the data that we have. I mean everyone's saying that there are no data about whether CTC will improve compliance, and it's one study. It's not a lot of studies, but I think that we have to be fair in saying that we have, as you said, look at the data we have, right? You don't think that's data?

DR. IMREY: No, because my understanding in terms of response to the question I asked previously is that this simply counting and adding --

DR. APPLEGATE: Right.

DR. IMREY: The bottom line is simply adding to the figure in the top line --

DR APPLEGATE: Right.

DR. IMREY: -- the folks who got CTC in the same group. It is not a comparative study of a willingness to get -- a willingness to get screened. It's simply an accounting difference. And I asked him if it was

purely an accounting difference, and he said it was. So I don't think that's a comparative study.

DR. APPLEGATE: But all it is, is a screening rate, right? And it looks like there's a higher screening rate in the folks that got the CTC.

DR. IMREY: But that's only by -- because the difference between in the rows isn't all for definitions of screening. The first row excludes CTC. People who got screened as CTC in the same group are included in the lower row and excluded from the upper row because CTC was not part of the upper row's definition of an adequate approved screening technology.

DR. APPLEGATE: So it's really not a --

DR. IMREY: So it's really not a -- no, it's not a, it's not a --

DR. APPLEGATE: All right.

DR. TALAMINI: So let's at least call it an open question.

DR. APPLEGATE: All right. But at any rate, I wanted to also speak to what we know about access and the -- what we know from mammography screening. And we do know that if we take away the co-pay, which the Accountable [sic] Care Act has done, we know that our screening rates have gone up nationally, regardless of where you practice geographically. There is discrepancy in geographic rates, but we know that those rates go up.

So as Dr. Kelsen asked earlier, will the rates go up, we don't

know. Well, I think we can estimate or predict that they will go up because there should not be a co-pay for a screening test that has proven efficacy.

The other point I wanted to make was -- I have one more point. We don't know the maturation of CTC because it's a new test, and we're trying to compare a newer test to an older test, optical colonoscopy. And so, I just want to remind everyone that, yes, optical colonoscopy is more mature and there are more data on it, and it is both diagnostic and therapeutic, no doubt. However, you know, CTC hasn't been around as long, so just to make an argument that CTC doesn't have data on follow-ups is because it hasn't been around as long. So I think we need to know what those are and we shouldn't close the door to what -- we need to know that and we want to make it available to make us understand it.

DR. TALAMINI: Thank you.

Microphones off when you're done talking. Thanks.

Dr. Glassman?

DR. GLASSMAN: Len Glassman.

Sixty-seven is the new 40, and 80 is the new 60. Medicare patients aren't acting as old as they used to. I was 67 last week. That's why I picked that number.

(Laughter.)

DR. GLASSMAN: I think that patients are in better physical shape. They're younger. I think the data on 55-year-olds and 50-year-olds is

logically applicable to the Medicare age group, not every single Medicare patient, but most of them. And I don't think we should be overly concerned that it's a different patient population when it comes to testing for colon cancer.

In the hands of experts was said a little while ago for CTC. I think we've also learned in the last few minutes that that probably should be said about optical colonoscopy as well. The data for optical is from the experts without a real gold standard to measure it against, but it's there. The data for CTC is from the experts.

I think in the last couple times I've been on panels like this where we've done new techniques or devices, one of the FDA's role was to mandate training. Now, I don't know if the FDA needs to do it or the American College of Radiology, but we shouldn't make the mistake that the GI people made, which is allowing anybody to buy a scope and stick it wherever they want. And I think that we can control quality somewhat with training. Thank you.

DR. TALAMINI: Thank you.

So, we need to start driving towards the close of the discussion about 1a, so we're now looking for fairly dramatic different opinion, and we need again to be brief and focused.

Dr. Shapiro.

DR. SHAPIRO: I am Jean Shapiro from CDC.

I just wanted to say that we need to consider that there are other alternatives to colonoscopy other than CT colonography. And so, patients, if they're also offered the options of an FIT test or a high sensitivity FOBT, I think it's unclear whether they -- which test they would choose, if they're unwilling to do a colonoscopy. And we have to consider that if the patient knows that they have to do the prep and they may have to re-prep if the CT colonography is positive, that they make another choice. And the burden is then higher.

DR. TALAMINI: Thanks.

So, let me just pause for a second and try and form some sort of a consensus. It sounds like in general the Panel is saying that they do believe there's benefit in the CT colonography, and most believe that it can expand the screening pool, but there are -- there remain a number of significant concerns about specific aspects.

And I would say that if you disagree significantly with that consensus, please add to it or change it at this point.

Dr. Shiels.

DR. SHIELS: Are you suggesting that the outstanding questions should preclude the option for the patients?

DR. TALAMINI: No. No, no.

DR. SHIELS: Okay.

DR. TALAMINI: Everything that everybody here has said is on

the record. And that's of great importance and is the greatest value of what we're doing. But at the same time we also, if possible, want to form some sort of a consensus so that we can move to the next question. But I want to make sure that issues all get aired here. So if what's been said so far or that consensus leaves some important elements out for 1a -- because we still have (b) and 2 to go -- now's the moment.

Yes, sir?

DR. SHIELS: Just the only -- two other additional points. Number one, again, having dealt with this now three times, this colonoscopy, to give the Medicare population an option to not to have somebody pulled out of work to come and accompany them for a day, or take themselves out of work for a day to have their colonic screening done, is a great option, if you can reduce the financial burden on people.

And the other one is a reality, and particularly with I think the Medicare population, and that is the fear of anesthesia. There's a real fear of anesthesia and a real fear of sedation. If they have an option to avoid that anxiety and that panic issue, then we should at least give them the option.

DR. TALAMINI: Thank you.

DR. Ziskin?

DR. ZISKIN: I just wanted to make a comment about increasing the number of -- enlarging the pool of people for the study. And Dr. Fennal had mentioned about when people are presented with the possible choice of

what to take, they don't really understand what the physician is saying at the time. And I think that's true. However, all the patients know about the preparation for the bowel cleaning and so on. And this is the thing I think that is the most disagreeable part of the entire procedure.

If the electronic stool extraction algorithm could be improved to the point where that becomes useable, I don't think there'd be any question of what people would choose as far as what to take for an option.

DR. TALAMINI: Thank you.

I'd like now to move to 1b unless there's -- oh, there's some burning comments. Okay.

Yes, sir?

DR. IMREY: Just to -- an amendment, and I apologize if I missed this. It seems to me that a statement about comparable efficacy should be tempered by some indication that this applies to the larger size polyps and that efficacy degrades at some level. And it might be drawn -- I would probably draw it where Dr. Ahlgren does at 8 mm, but one could draw it at 1 cm.

And I think we should also say that this is on the basis of the best available -- best currently available data and not leave it as an absolute statement of blanket effectiveness. Because I think that may -- the standards may change, and we learn more about the significance of the smaller lesions in the future, and we ought to have this in our statement.

DR. TALAMINI: Yeah, again, the value of this meeting is exactly that set of comments, including that one. We don't need to drive to an exact statement or a vote.

Other comments?

DR. ZHOU: I want to say that that's true. We make decision based on the data, but we have to say something about quality of the data so that people understand that our decision is -- that we don't want people to get a way to say, well, that data is perfect. But I think we need to say some statement of the data, quality of data.

DR. TALAMINI: Okay. I'm going to move to 1b at this stage. We're not done with the discussion, but I want to move to the safety issues. And if you read point number 2, there's another opportunity to discuss risks and benefits.

So, 1b says, again, considering available colorectal cancer screening tools and current colorectal cancer screening recommendations, please discuss the currently available data and information on:

b. Safety issues related to the use of CT colonography for the screening of asymptomatic patients for colon cancer, including radiation risk and extracolonic findings.

So, who would like to begin speaking to the risk? I think we'll begin with Dr. Kelsen.

DR. KELSEN: Thank you. Dave Kelsen from Sloan-Kettering.

I'll just parenthetically say I'm a medical oncologist, a GI oncologist, and any surveillance and screening program that decreases the chance of seeing me or Dr. Ahlgren is meritorious.

So from the safety point of view, I think that data that we heard from several speakers is that the radiation risk for a single test given once every five years is very low, very low, and maybe even below of the level of even measured. And although there's no radiation with OC and there's no radiation with fecal occult blood, and so, by definition they have less risk, measurable or not, the radiation risk is extremely small for a one-time CTC.

And we also heard, I think, that if you use a structured report on extracolonic findings and you sort of spell out to a guy like me don't worry about this or you really, really should worry about this, it would significantly decrease the number of unnecessary follow-up tests. I think there is uncertainty about that. I don't think they really gave us -- I mean the numbers were all over the place. And when I see 5% to 50%, if you do an unstructured report, you'll bring it down to a low level; I think basically it would be if you're very careful, it will be acceptable. But I believe that this is also an area for future study.

Nonetheless, the data they presented to date with careful reporting, follow-up for extracolonic events that are not necessary should be limited. And that probably loops back to this training comment we heard earlier that like with any new technology, you're going to have to train

people. And I really take to heart the expert question that was raised earlier. At the beginning when you guys were starting to do OC, there were not a lot of people doing it, and you had large training programs, and now you have a lot of people doing it. And experts do it really well, and people who aren't experts probably don't do it so well.

So I think the sum is that the risks are far less than the benefits.

DR. TALAMINI: Thank you.

Dr. Afifi?

DR. AFIFI: Thank you. The statement was made several times earlier today that there is no gold standard, although it seems that the comparisons that were made of CT colonography was always versus optical colonoscopy. So I'm thinking that the real comparison we're looking for here is between those two. The side effects or the potential risks of CT colonography are in my mind two things. One is the dangers of radiation, and the other is the false positives with the extracolonic findings.

I haven't really heard enough about what are the potential dangers of optical colonoscopy, but apparently the perforation seems to be a concern. So a comparison of radiation potential harmful effects -- and we have to keep in mind that those are calculated really on the basis of mathematical models that make a lot of assumptions. I, since 1975, have been doing research in that area in the context of non-ionizing radiation, electromagnetic fields. The same issues come up, and it's still an open

question.

So as far as comparing then the harmful potential side effects of CT colonography versus optical colonoscopy, we really don't know the answer to that. And I do have some comments then about how to combine that into a risk/benefit calculation, but maybe I'll wait until we get to Question No. 2.

DR. TALAMINI: Okay. Thank you, Dr. Afifi.

Dr. Nostrant.

DR. NOSTRANT: I was going to say just two things. I've seen a report of benefit versus risk, but I think when you have multiple screening tests, it has to be excess benefit and excess risk over the other screening process. So if you're using FIT as an example and we say FIT is going to have that same 95%, the CTC would have to be greater than that benefit. You can't just use obviously expected benefit of a single test versus doing nothing, which is what is being presented in the slides. It really has to be presented as excess improvement.

So let's assume 2.5 or 4%, which is we what see over colonoscopy, and the argument would be that that might not be enough to warrant the risks that I see with radiation exposure and also the cost, which appears to be 1 in 200 people. You're going to be doing 198 more tests for more extracolonic findings. So I mean it seems like a large number -- cost. And then potential surgical intervention on those things when there's a false

negative has to be put into the excess risk and benefit, and we don't have that data so far to date. That's all.

DR. TALAMINI: Although our task is not to consider cost.

Dr. Dauer?

DR. DAUER: Regarding the radiation, I think we had a very good report today. We'd all agree that the dose for CTC is probably not much more than what we get annually as our background radiation anyway, and it shouldn't be a problem. As far as we heard some discussion earlier about the young people get CAT scans and then we accelerate the dose and everything -- it adds up, we're talking about people over the age of 50 having their first CTC, not 30-year-olds having CTC. So if you start at 50, 55, 60, your risk goes down of developing a cancer as you get older.

Our best experience that we have are the atomic bomb survivors. We heard earlier there's about 100,000 survivors that survived the immediate blast and heat effects that were studied for many years. The last time that a report came out summarizing what's happened with them was 2006. And of those 100,000 people, 40,000 were still alive in 2006. They did a study of how many excess cases of cancer -- not cancer mortalities, but how many excess of cancers were found in those survivors. And of the 100,000, other than the children that died early from thyroid cancer, there were only 465 excess cases of cancer out of 100,000 people.

So I think the risk is very, very small. And it's probably offset by

the extracolonic findings that we're going to be able to discover. Now, I know you're talking about doing these cases, extra studies and things. In our material we saw some statements that said, well, you can scan abdominal ultrasounds by -- abdominal aneurysms by ultrasound. Well, the reality is people do not get scanned for their aneurysms by ultrasound. That's not a test that is done unless the patient is symptomatic. People do not get scanned for their hypernephromas by ultrasound. They're picked up as incidental findings on other studies, such as for gallbladder or pancreas.

So I think that for radiation, the risk is very, very low. It's going to get even lower as we go along and it's going to be -- ultimately I believe it will increase the number of patients that will end up having the colon cancer screening. And then, the potential offset from the ECF findings of unnecessary surgery and unnecessary workups is going to be offset by the number of cases of people that you're going to save early on from an aneurysm. We all know what an acute leaking aneurysm looks like in the emergency room setting.

So I think that if we limit it to age 50 and above as one of our criteria -- and then I'm going to talk further in No. 2 about quality assurance and accreditation of facilities, which I want to bring up, I think that it's something that really needs to be given as an option. Thank you.

DR. TALAMINI: Thank you, Dr. Dauer.

Dr. Glassman.

DR. GLASSMAN: Len Glassman.

We heard this morning the data about radiation risk. That was for a dose of 6-7 mSv. We also heard this morning that actual dose today is 3 mSv. Under a linear model that was used, that halves any theoretical dose. So it's half of what we've been considering this morning that we heard about, one.

Two, the extracolonic findings are the cherry on the top of the sundae for colonoscopy, for CT colonoscopy. They're the lifesavers that we didn't expect to get. They're the small renal tumors. They're the abdominal aortic aneurysms. They're the person who goes to the emergency room knowing they have a left renal stone, or even better a right renal stone, rather than acute cholecystitis, because they were told from this test. Those are pluses not minuses.

DR. TALAMINI: Dr. Isaacs.

DR. ISAACS: Kim Isaacs.

One thing that we haven't mentioned in terms of risk are the miss rates, and that's miss rates actually for both studies. And I guess the big concern that I have after listening to all the data that we just don't know yet is those small lesions. We were shown some rather impressive growth characteristics over a four- and five-year period, and I think that the -- we're going to have to see what happens over the next 10 years with some of those smaller lesions to find out their clinical significance. But I think that that

needs to be considered in risk.

DR. TALAMINI: Dr. Fennal, I hate to call on you, but any specific comments about risk? If not, that's fine.

DR. FENNAL: Mildred Fennal.

I don't have any -- not specifically about the risk itself, but one of the things that I wanted to say was that when we -- if you offer me a test, if you offer me to have one or the two tests, and I figure out that if I'm 50 years old, I have to have four colonoscopies versus eight CTCs, the probability is that I'm going to accept the four.

DR. TALAMINI: Okay.

Dr. Steinberg.

DR. STEINBERG: So in terms of (b), I can't talk about the complications or the down side of CT colonography without talking about the down side of colonoscopy because that's your major competitor here. And if you look at the complication rate, CT colonography wins straight out. The perforation rate is high enough to -- from colonoscopy is high enough -- by the way, Dr. Afifi wanted to know the other complications. There's bleeding if you take polyp out. There's aspiration. There's too much sedation. Many colonoscopies are now done more with conscious sedation.

By the way, Dr. Shiels, if I ever heard of an advertisement for propofol sedation, you're it.

(Laughter.)

DR. STEINBERG: You're the poster child because we don't have patients complaining of discomfort any more doing propofol.

So the perforation rates are high enough to overwhelm all the smaller complications you're talking about from CT colonography. I want to point out though from the numbers, for every important lesion that you find on the extracolonic findings, if I got those numbers right, there are 30 -- for every 1, there's 30 that require a workup that may worry the patient, may cost money, and don't result in an important finding. Yes, finding a renal stone is nice for the patient to know about.

But I take care of a lot of pancreatic cysts, and we know now by screening the population, a certain percentage of them have these small cysts, which then require -- you know, it goes on and on for a cycle that is forever, as far as I could tell, of worrying and re-imaging these patients. So if I got the numbers right, for every 1 really important extracolonic finding that requires surgery or something, 30 -- there are 30 that don't. And so, I don't think that's a game changer for me in terms of the down side of CT, but it has to be factored in.

DR. TALAMINI: Dr. Pinsky?

DR. PINSKY: I would just say in terms of extracolonics, I think with our experience, certainly with cancer screening, we can't really assume that finding a cancer early is beneficial. We've got a lot of counterexamples for that, so I definitely would not say that any time we find an extracolonic

cancer, that you're necessarily doing good and you're not possibly doing harm. That being said, I don't think it's a major negative. I think it'll hopefully play itself it out, and there'll be an equilibrium of what's worth working up. But I would just caution to saying that it's automatically a positive when you find a cancer early.

DR. TALAMINI: Okay.

Dr. Imrey? No?

Dr. Ahlgren?

DR. AHLGREN: If I can address the radiation issue quickly, by agreeing that it's not a major risk. But it is risk that exists because it's not insignificant compared with the number of these procedures that are necessary to detect one colon cancer, to save one life from a colon cancer. Really the number we should be concerned with is the number of cancers found per potential secondary cancer due to the radiation. And it looks like that number is up in the 20s at least. So we're not offering this as the standard procedure. We're offering it as an option. And if offering it as an option brings more patients in who will be screened and have cancers detected, then certainly the benefits outweigh that particular risk.

One other thing that I think needs to be said is that we're not offering -- we should not be offering this option in a vacuum. We have to recognize our duty as physicians to educate our patients and to make sure that they understand the full implications of each of these studies: what they

will go through, the fact that CTC is not a diagnostic procedure, it's a screening procedure, and that some -- depending on their age, 10 or 20% will have a finding that will require optical colonoscopy. And they have to understand that they have to do that in order to get the benefit of the CTC.

DR. TALAMINI: So, just to pause for a second, it sounds like the consensus that's emerging is that the benefits of potentially expanding the screening pool outweigh the small risks, in this committee's opinion, in general of the radiation risk. On the other hand, with respect to the extracolonic findings, it feels to me like a wash. About half the Panel has great concerns. Another half of the Panel thinks there's great advantage in finding lesions that might not have already been found.

That seems to me to be what's emerging. So as we go forward, let's speak to that potential emerging concept.

And next was Dr. Charabaty, I think.

DR. CHARABATY: I don't remember what I wanted to say, but talk about extracolonic findings. I think just to agree with my colleagues, you're always going to find good stories where somebody went for kidney stones and they found a pancreatic mass. But it doesn't mean that's going to decrease mortality from this pancreatic cancer. Otherwise -- I mean I don't know of any society recommends total body CTs. We have all seen people doing total body CTs, but we don't recommend them because we don't know if finding lesions earlier will actually make a difference.

So I think for me, the extracolonic findings are not part of the discussion because really our focus should be detecting colon cancer or colon polyp and decreasing incidence of mortality from that.

DR. TALAMINI: Dr. Lurie, I think.

I'm sorry, Dr. Kelsen.

DR. KELSEN: It's okay. I'm not sure that I would agree that there was such a dispute between the Panel members or disagreement as to whether finding extracolonic manifestations of X or Y are bad or good so much as that there's uncertainty. I think the reflection that's coming back as I listen to the Panel discussion is I don't think we actually know whether it's in the end going to be a good thing or in the end it's going to be a wash or in the end it could even be a bad thing. And it would be -- it might not be a bad thing to highlight that the Panel discussion suggests that there is a -- that's a significant area for research as this procedure becomes more widespread for prospective collection of data.

DR. TALAMINI: Well, and at least one -- I appreciate that. At least one comment was that using strict criteria would be important for those extracolonic findings. And I think we did have consensus on that concept.

Other comments with regard to risk as we drive this one to the ground? Yes, sir?

DR. IMREY: I think that the risks associated with the pursuit of extracolonic findings do have to be included in our considerations because it's

the patient that we're treating. I'd like to add one comment on risk and then make a friendly amendment to your tentative statement of balance.

The comment I'd like to add on risk is -- it's something that's come up in the discussion from a couple of people before -- is the suggestion that our assessment of this technology and this use should be somehow modulated by the amount of additional radiation that patients are being exposed to for other reasons, therapeutic, diagnostically, whatever. And I actually don't think that should be a consideration on our part unless there's some reason to believe that the impact in terms of generation of additional cancer cases -- the marginal additional impact generated by the use of CT colonography increases based on past patient exposure so that more cases are generated by a given dose for CT colonography in a patient who has had 100 extra mGy than in a patient who has had only 10 prior mGy.

Then I don't think that -- unless that's the case, I don't think that the patient's other exposure to radiation should have any impact on what we do. We can't decide that we're not going to use a technology for the benefit of patients just because other people are using it for their own good reasons unless one use biologically changes the patient's response to the other use. And I haven't heard evidence for that.

I would like to add to the tentative statement balance a consideration. I yielded the floor before because Dr. Steinberg had more or less stated my comments, but I want to bring it back because it went away --

and a couple of other comments.

I think we've tended to emphasize the discussion of radiation risk, but deemphasize the discussion of colonography risks, and yet we know much more about colonography risks than we do about -- excuse me -- about colonoscopy risks than we do about radiation risk. We know a lot more about perforation risks than we know about -- a lot more about bleeding. We've got a lot of experience with that. And it appears to substantially outweigh by an order of magnitude our best estimates of radiation risks that we have at the moment.

So I see as one major advantage potentially of increased use of colonography the reduction in colonoscopy risk. And there will be reduction on colonoscopy risk for all those patients who undergo colonography and are not referred upwards. And I think that belongs in our statement, as well as the potential advantage of colonography of increasing participation rates.

DR. TALAMINI: Ms. George?

MS. GEORGE: This is Elisabeth George.

I think a couple people made the comment about the radiation, and I actually applaud everybody's comment on it. I did want to re-remind people, as Dr. Glassman stated, is all of the data that we've looked at it was at 7-10 mSv. We're right now at 3 with many people actually down at 1. And industry as a partner with probably everybody sitting at this table and many people out in the audience has been working on continual reduction,

continual warnings, continual monitoring.

So I think that that risk really is almost nonexistent, as was stated earlier. But I do think we do have to at least be aware that all of the imaging modalities are being used at an increased rate for all different things. And if we are going to be doing due diligence, we do want to at least keep that in the back of our minds.

DR. TALAMINI: Dr. Nostrant?

DR. NOSTRANT: I guess I would bring up the fact that remember CT colonography also has a risk for perforation related to colonoscopy and polypectomy. You're going to be sending people for those, and you have to assume that risk too because that test is being done for the purpose of doing CT or polypectomy. So I agree that we will likely reduce in an average-risk, low-risk patient the risk of colonoscopy and perforation, colonoscopy and bleeding. But remember there's still 30 or 40% high-risk patients in which you're going to expose those high-risk patients to a dual procedure. And, therefore, that risk has to be assumed too by the CT colonography if you're going to talk about actual risk.

DR. TALAMINI: Dr. Isaacs.

DR. ISAACS: Kim Isaacs.

I was just going to comment on the bleeding risk. That person is not going -- like Tim just said, that person's not going to obviate the bleeding risk because if they're bleeding from a polypectomy, they would

have gotten there anyway with the -- based on the results of the CT colonography.

DR. NOSTRANT: And one last thing. Remember we're comparing apples and oranges too with colonoscopy. We've not discovered anything -- discussed anything about what's new in colonoscopy in terms of both diagnosis -- diagnostic accuracy and also prevention of complications. We're not talking about clipping. We're not talking about endoluminal repair. We're not talking about any of those things, which are not routinely done by colonoscopists when they have a concern about the risk for bleeding or risk for perforation, so I think it's difficult.

And that's why I think when we talk about state of the art, we have to talk about state of the art for everything and why we have to talk about excess benefit over excess risk, not presume benefit versus doing nothing because I don't think that's a good way to do it.

DR. TALAMINI: Dr. Dauer.

DR. DAUER: Very early today, I think we all remember the nice slides with the National Council of Radiation Protection report showing the pie-shaped chart comparing 1980 radiation levels to the population to that of 2009. So in 1980 we were doing only a 3 or 4 million CAT scans a year and the dose to the population was 3 mSv. In 2009 it became 6.2 mSv, and we were doing 70 million CAT scans a year.

But I don't want that to mislead you because none of that

increase in radiation is from the CAT scans. Granted, a lot of the increase in nuclear medicine studies and CAT scans came in, but you have to understand that 17% of that radiation dose that you did not have 1980 was from interventional procedures, such as interventional neuroradiology, cerebral artery aneurysms, clipping, vertebroplasties, kyphoplasties, procedures that are really, really beneficial to the patient but have a lot of radiation.

There's also a number of those studies came from the advent of positron emission tomography. So just because we went way up in CAT scans and we doubled the dose to the population, I don't want that to be misleading that there weren't some beneficial aspects of increased utilization. I still believe we do too many CAT scans, and we all agree we shouldn't do screening CAT scans for whole body and things like that. But there are a lot of good things that caused that radiation level to go up.

DR. TALAMINI: Dr. Imrey.

DR. IMREY: Just very briefly to the point about bleeding from polypectomies. If you do a CT colonography and you don't even report small polyps and you do colonoscopy and you clip three or five 3 mm polyps, then you have a substantial difference in risk associated with the bleeding from the polyps that you're clipping in one screening modality and not even reporting in the other screening modality. So you're not referring upwards, and that's the issue.

DR. CHARABATY: But these are very low risk bleeding for the

small polyps, so really when we talk about bleeding post-polypectomy, this is really for larger polyps. So for very small polyps, the risk of bleeding will be really close to zero.

DR. IMREY: Okay. If that's the case, then I stand -- reduce that concern.

DR. TALAMINI: Dr. Shiels.

DR. SHIELS: Just very briefly, not to argue with the Chair, but you mentioned that the issue of the extracolonic findings was a wash. I think if we can prevent 2,500 preventable deaths in a 100,000 people, that's not a wash. The second point is, is that if we have incidental findings like pancreatic cysts, good doctors who are well educated and understand how to work up cysts -- just like mammography screening finds simple cysts -- we don't have to stick a needle in every single thing we see.

So if we have good education, we can avoid unnecessary intervention, unnecessary tests, if we use the findings appropriately, and save some people who have aortic aneurysms before they die.

DR. STEINBERG: I'm going to have to answer that.

DR. TALAMINI: I was, of course, not expressing my opinion because I'm a surgeon.

(Laughter.)

DR. STEINBERG: So surgeons are not included in this discussion. But pancreatic cysts are a major problem whether you stick a

needle in or not because none of us feel comfortable writing them off. They have to be followed, and we don't know the proper interval, and we don't know what happens to them. So it is a source of -- it's a big headache.

DR SHIELS: But I hope as a panel for the FDA and the American public, we're not suggesting that we should run around and ignore disease that might kill us.

DR. TALAMINI: No, I think the best term was -- wash was inartful. I think the best term is uncertainty. I think that's a better term.

DR. AHLGREN: Do we prefer not to know?

UNIDENTIFIED SPEAKER: Right. That's the point. Let's not delude the public.

DR. AHLGREN: It's like saying we don't want to know.

DR. TALAMINI: Yeah. Well, I think with respect to the opinions of the Panel, though, there's uncertainty about the value of the extracolonic findings versus the risks, in the context of risk.

Dr. Jiang, opinions regarding risk?

DR. JIANG: In my mind the risk is not a big deal. The -- risk, I think it's there, that's my concern. But I heard a lot today that minimized my concern there. The extracolonic findings is a concern, but I heard there's benefit in that, and that's a surprise, so I'm not so much concerned about that.

The question just brought up whether we don't want to know; I

think that's a key question. OC, you don't know that because you don't get to see it. CT, you get to see it. The question is do we really don't want to know. In some situations that's a legitimate question.

DR. TALAMINI: Okay. Thank you.

So, any other comments with respect to risk? If not, I think what we'll do is move to Question No. 2. And for this, since this is sort of a summary question regarding all that we've heard today, I think we actually will go around the room and ask everybody to make at least a brief comment regarding No. 2, and unfortunately will need to be brief, but we'll get everybody's opinion.

So No. 2: Given the risks and benefits identified, please discuss your views on the role of CT colonography as one option for screening asymptomatic patients for colorectal cancer.

And we will either get Dr. Imrey or Dr. Kelsen to begin. Do you guys -- either one of you have a strong -- all right, sir. Dr. Kelsen. And then we'll go counterclockwise around the table.

DR. KELSEN: Dave Kelsen from Sloan-Kettering.

So I think that the risks and benefits as identified today would make me say that CTC should be one option for screening asymptomatic patients for colorectal cancer. The pickup rate is high enough. The safety issues have been addressed. I would say that neither OC nor CTC do not have sufficient participant rates, and that's been a big source of discussion today.

And it's striking that there is another technology, namely measuring stool, which has not penetrated acceptance, and that should be an area for significant discussion at probably a different panel to see how you could increase that participation rate. But CTC should be included as an option for asymptomatic colorectal cancer patients.

DR. TALAMINI: Thank you.

Dr. Ziskin.

DR. ZISKIN: All things considered, I think it should be an option.

DR. TALAMINI: Thank you.

Dr. Shiels.

DR. SHIELS: I could second that. I think it's a critical option to give patients the opportunity to detect a life-threatening disease. And the second part of that, I think it's very important -- very similar to the way the FDA handled the Mammography Quality Standards Act, and that is to build in standards for quality assurance, quality of training, and accountability performance after the fact.

DR. TALAMINI: Thank you.

Dr. Ahlgren.

DR. AHLGREN: I agree with -- I echo your statement.

DR. TALAMINI: Microphone.

Dr. Steinberg.

DR. STEINBERG: So, given that question, my answer is yes, it

should be one of the options. I don't think it's going to seriously dent the number of people who are going to be screened. I concur with what Dr. Fennal said that the majority, the great majority of people who are not being screened are not being screened for many other reasons and not all the choices.

And one other thing about clinicians offering the choices is time. You have a certain amount of time for a patient interview and to go through all the choices and the pros and cons is just -- it's not going to be done. The only way these choices actually come up is if the -- if I'm a gastroenterologist and I get referred from a primary care for a colonoscopy, I go through a colonoscopy. I don't go through all the options. And I bring them up if the patient brings them up. So then we're going to have a discussion, the pros and the cons of a virtual colonoscopy versus this colonoscopy. I don't even include FIT and flexible sigmoidoscopy and the data. That's assuming I know the data. And I learned a lot of data from this conference, so it's a very difficult --

DR. TALAMINI: You go to a barber and you get a haircut, right?

DR. STEINBERG: What's that?

DR. TALAMINI: You go to a barber and you get a haircut.

DR. STEINBERG: That's right. But in answer to this question, given what we have, yes, it should be offered and it should be paid for by insurance. The big outstanding insurance that doesn't cover this is Medicare.

And they really have to come to the plate here.

DR. TALAMINI: Dr. Jiang.

DR. JIANG: I agree. I think the option should be made available. I think the benefit seems clear, and the risks seem to be not overly great at this point. I think that should be followed with quality control and training. I just want to point out that we really shouldn't push the option -- the decision to the patient. That's a big burden for the patient to make that decision.

MS. ALDRICH: Dawn Aldrich.

I do agree that the CTC should be a part of the patient's ability to choose.

DR. TALAMINI: Thank you.

Dr. Isaacs.

DR. ISAACS: Kim Isaacs

I think that the discussion that we've had with CTC and OC, both of them -- I think they're complementary. And I think that there are clearly patients who we need to have this option for, including patients on anticoagulation, patients who might screen with an OC that -- I mean with a CTC that refuse an optical colonoscopy, those who have incomplete colonoscopies, patients who have significant contraindications to sedation.

And also, what was brought up earlier by our very first speaker -- actually, we may increase availability of colon cancer screening in

areas where optical colonoscopy is not available, where there are not gastroenterologists, by using some of the telemedicine concepts that were brought up with the first speaker.

DR. TALAMINI: Thank you.

Dr. Glassman.

DR. GLASSMAN: Len Glassman.

I agree that it should be offered. I also think that training for any new procedure is important, and it should have an important role in improving the quality of CTC.

DR. TALAMINI: Thank you

Dr. Zhou.

DR. ZHOU: I also agree that CTC has a low risk and has a benefit and can be an option. But I want to emphasize that we don't want to make that forced on the patients so that the patient has an option to choose which screening tool to have. And, in addition, I want to emphasize that even though the data was presented to us, we cannot change it, but I have some question about validity of the conclusions based on the population results because of the gold standard they used there.

DR. TALAMINI: Thank you.

Dr. Foxx-Orenstein.

DR. FOXX-ORENSTEIN: Amy Foxx-Orenstein.

I feel that colonoscopy should continue to be presented as the

optimal screening tool for both its diagnostic and therapeutic potential, and that CTC should be an option in the armamentarium of screening, and that we all need to do a better job of educating our patients.

DR. TALAMINI: Thank you.

Dr. Dauer.

DR. DAUER: Edward Dauer.

We cannot forget the word asymptomatic. I think it's got to be limited to asymptomatic patients, and it's got to be limited to those over the age of 50, unless they had one of the reasons they couldn't have a conventional colonoscopy, such as anticoagulation, and we've mentioned a lot of those before. So I think there should be an age limit for screening. I think it should be covered by insurance companies.

I would like to see the USPSTF look at the newer data and articles that are out there and perhaps update and meet on that topic again, as I believe CMS should look at the new data. I would like to see -- we mentioned over here what they did with mammography for MQSA. I think that the facilities that offer mammography today -- you know, they have to be accredited. I think that we shouldn't allow CTC to be performed on Medicare patients -- and probably insurance companies would follow with that also -- unless the facility is accredited and the reader is accredited.

And you notice I didn't say radiologists, so I'm not -- I'd like to see radiologists do it, but not everyone who does colonoscopies is a

gastroenterologist. So I think that the reader should be accredited by a federal agency and the facility. And part of that accreditation should not only be quality control and follow-up of the patients, but also a very, very important -- informed consent as to the risks, such as the radiation, and their options and other ways that they can be screened.

And I also think that if we're going to do routine screening for the asymptomatic patient, it should be limited to no more than once every five years, again, unless there's a medical indication that has to be documented in the medical record why it needs to be done more frequently and it could not be replaced with a conventional colonoscopy.

DR. TALAMINI: Thank you.

Dr. Shapiro.

DR. SHAPIRO: I agree that there is a role for CTC as an option for screening asymptomatic patients who are not at high risk for colorectal cancer. We haven't really discussed what the options should be for high-risk patients such as those with a strong family history, but CTC should be an option for those who are not at high risk.

DR. TALAMINI: Thank you.

Ms. George?

MS. GEORGE: Obviously I agree that CTC should be an option. I think it's a -- having the choice, as people stated. I also do like the ideas that were mentioned about the assurance of training. I think that should be for

every medical device that the user needs to understand how to use it. We don't develop those user instructions for our health. We develop them for the patient's health. So I think that is important. And if accreditation is looked at, I think that all the stakeholders should be engaged in that discussion. It shouldn't just be one or two people making those decisions.

DR. TALAMINI: Thank you.

Dr. Pinsky.

DR. PINSKY: I think CTC should be an option. I think we have to remember there's a timeframe element, and we're talking about the every 5-year CTC versus every 10-year OC. I think there are some relatively minor concerns about the sensitivity for 6-9 and under 6. And I think that's mainly obviated by having every 5 years instead of every 10. So with the every 5-year, I think they're essentially equivalent. I don't think the evidence is there really to be able to go to 10 years with CTC with the concerns about the sub-10 and the sub-5. And I think the safety risks certainly in terms of radiation are minor.

DR. TALAMINI: Thank you.

Dr. Fogel.

DR. FOGEL: I agree with what Dr. Dauer said. I think that CT colonography should be one of the tests offered to the asymptomatic patient undergoing screening procedures. I agree with the concept of accreditation of the facility, documented training of the reader, who doesn't necessarily

have to be a radiologist, but the concern that I have is that the test will be used inappropriately. And I think that along with what we've talked about, we need to develop clinical decision rules that will direct the primary care physician to make sure that the appropriate choice is made, since we believe that it's the primary care physician's responsibility to make the choice, not the patient.

DR. TALAMINI: Thank you.

Dr. Coldwell.

DR. COLDWELL: I believe that CTC should be expanded and that it should be one of the options for screening. I also heartily agree with the comments made about using this as similar to MQSA and accreditation.

DR. TALAMINI: Thank you.

Dr. Norstrant.

DR. NORSTRANT: I think that CTC should be an option for patients particularly in those patient groups for which there is -- that colonoscopy is a bad option, but also should be an option as a primary diagnostic tool after a properly informed patient and a properly informed referring doctor.

DR. TALAMINI: Thank you.

Dr. Fennal.

DR. FENNAL: Given the risk and benefits identified, I believe that CTC should be part of screening for colorectal cancer, but as an option

when non-invasive methodology or a colonoscopy are inconclusive or cannot be completed. I also support explicit training for performance as well as interpretation of test results among physicians.

DR. TALAMINI: Thank you.

Dr. Afifi.

DR. AFIFI: I look at this from the -- point of view, and I believe that given all that we have heard today and all that I know about the subject, that indeed CTC should be one of the options that's available. Having said that, I think also the primary care physicians need to quite well educated in that question because most of the time they're the ones who are making the recommendation, in which case the choice then would depend on how high a risk the patient has of having colorectal cancer. For a high-risk patient, then, the optical colonoscopy would be the choice because any polyps found would be also eliminated during the way. For average- or a low-risk patient, the CTC and the OC would be both options that the patient can choose from.

DR. TALAMINI: Thank you.

Dr. Charabaty?

DR. CHARABATY: Aline Charabaty.

I believe that any screening is better than no screenings. And with the CTC, it obviously shows that it has good sensitivity and specificity in detecting significant polyps, so I do think it should be one of the options. However, I do think that the colonoscopy still has something superior to all

the other tests in that it's diagnostic and therapeutic. And I still feel that that's the only test at this point that addressed the concern for serrated adenoma of the right colon. But definitely for patients who cannot undergo optical colonoscopy or they had an incomplete colonoscopy or a fear of colonoscopy, at least they have another option that's very similar to optical colonoscopy.

DR. TALAMINI: Thank you.

Dr. Applegate.

DR APPLEGATE: Kimberly Applegate.

I also believe that CTC should be an offered option for asymptomatic patients to be screened from age 50 at the currently recommended intervals, and it should be a reimbursable imaging test. I also believe -- and I will not enumerate all of the discussion about the potential for research to help us better define the different tests that we've talked about, not only CTC, but OC and some of the other tests that particularly Dr. Kelsen has I think discussed in the greatest detail to understand which test is better under which circumstance and in which subpopulation.

DR. TALAMINI: Thank you.

And Dr. Imrey.

DR. IMREY: Peter Imrey.

I believe that CTC should be offered and available as a co-equal option with the other approved screening modalities for colorectal cancer,

but only in conjunction with pursuit of the quality control measures of accreditation and then standardization that others on the Panel have emphasized. I'd also like to associate myself with the distinction Dr. Afifi made between average-risk patients and high-risk patients for whom colonoscopy would be clearly preferred.

I'd also like to add that in the implementation of this and in addressing standards for referral upwards to colonoscopy, that consideration be given to developing registries or other means of tracking what happens to 6-9 mm polyps that are not referred upwards so that we can learn more about the biology of these lesions and improve our overall screening practices moving forward.

DR. TALAMINI: Thank you.

So I think with respect to Question 2, that it's the Panel's consensus that CT colonography certainly should be one option for screening asymptomatic patients with lots of discussion regarding quality control and many other issues that have been brought out by the Panel members, training, et cetera.

I want to specifically ask Ms. George, our Industry Representative; Dr. Mildred Fennal, our Consumer Representative; Ms. Dawn Aldrich, our Patient Representative, if the three of you have additional comments at this time.

MS. GEORGE: This is Elisabeth George. No, I do not.

DR. FENNAL: No, I do not. Thank you for the opportunity to serve.

MS. ALDRICH: No. Thanks.

DR. TALAMINI: And I would ask the Panel since we're drawing to a close here, if there are specific issues that you feel have not been brought out adequately to the FDA that you want to bring forward at this time.

DR. AHLGREN: May I ask a question?

DR. TALAMINI: Dr. Ahlgren, certainly.

DR. AHLGREN: Here we are a panel of gastroenterologists, oncologists, radiologists, specialists, discussing the various merits of CT colonography. But who is going to recommend to the patient -- the patient without symptoms -- the asymptomatic patient to have your screening? It's not us. It's going to be the general practitioner.

And how are we going to get the general practitioner to appreciate at least the basics of the issues involved -- if this were my patient and I said you should go get screened and here are the possibilities, he'd say, well, what would you do, Doc? What do you recommend? And he's got to answer that question. I don't know who is the proper -- what is the proper way to address that need through a professional society or how it should be done, but that needs to be done.

DR. TALAMINI: That's a good comment. Any other burning

comments?

Dr. Dauer.

DR. DAUER: I was impressed. We brought up briefly, but we didn't really discuss in detail the main problem we have today, it's not that any of us here can't get a colonoscopy versus a CT. It's the underserved population, which is I think our biggest problem. And how do we reach out to the people who have no access to the medical care?

And it was brought up before, and I thought it was a good idea, that perhaps if you can find some bill in Congress or congressional funding -- I know money is tight today, but if the government could get into the mobile CT van business and send these CT scanners out to the underserved communities where they have no access to this healthcare and have an allied health professional, such as a nurse practitioner that's licensed, or a physician's assistant to do the medical screening and history on these patients to make sure they're suitable, I think that would be a tremendous boon to our underserved population if we could now have all these studies done where there's no access with any methodology. And, of course, they could be read by teleradiology.

And I think that's something that -- you know, I know it's wishful thinking with the lack of money, but something I think you should think about.

DR. TALAMINI: So would you have the prep van go one day

ahead of the CT van?

(Laughter.)

DR. DAUER: I think what you do is you go into a community and you stay there for two or three days. And the first day you screen them and then you pass out the kits. And then you say we're staying overnight and come back tomorrow and we'll do the scans.

DR. TALAMINI: Dr. Jiang, comment?

DR. JIANG: Just a quick comment. I think the patient ultimately will make the decision one way or another in terms of screening. But we're sitting here all day listening to costs and benefits, and we can't make up our mind which one is easier. And I think it's just not realistic for the patient to come up with the right decision.

DR. TALAMINI: Well, that combined with the call that we've heard today for more data to make these decisions.

Dr. Lurie, closing comments?

DR. LURIE: Yes, thank you. Well, I think we can all agree it's been a really fascinating day of scientific discussion today. And I'm personally heartened by the idea that we can get specialists from so many different fields to come in the same room here, sometimes difficult to interpret data, and come to an agreement. I think that's just generally a hopeful sign, and I think that'll be very helpful to us going forward.

I think we've clearly identified what these -- and addressed

these central questions related to this technology. So let me just explain then what the process will be going forward.

There will be a short summary of this meeting, which we will put together. It will up on the web in about 24 hours. And then, some weeks after that, we receive a copy of the transcript, the full transcript of this meeting. We have to proof it, but that winds up on the web as soon as we can, so expect that within several weeks.

The advice that you have all provided will be provided to the Center for Devices and Radiological Health, and it will inform their ongoing regulation of this product.

I just want to close then by saying some thank yous, first of all, to the collective Advisory Committee members here. A large number of you came in from across the country, and thank you very much for a very provocative set of discussions.

I think our presenters, even by the often excellent standards that we have here at FDA, were particularly good today, and I think there were some really very, very clear presentations, and good answers to your good questions.

I want to thank the Open Public Hearing session speakers for coming and presenting their points of view in clear and persuasive fashion.

And, finally, I just want to thank an almost literally cast of hundreds here at FDA who helped us to put this meeting together. So thanks

again to everybody.

Dr. Talamini.

DR. TALAMINI: Thank you. And with that, this joint meeting of the Gastroenterology and Urology Devices Panel and the Radiological Devices Panel is now adjourned.

It looks as if we need to make an announcement that when the meeting ends, the cars are here, and that Panel members can leave expeditiously. And they should come down to the registration desk so they can be escorted.

So, again, thank you all very much for your time and attention.

(Whereupon, at 4:30 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

JOINT MEETING OF THE GASTROENTEROLOGY-UROLOGY DEVICES PANEL

AND THE RADIOLOGICAL DEVICES PANEL

September 9, 2013

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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Official Reporter

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